THE DIAGNOSIS OF PREPSYCHOTIC SCHIZOPHRENIA

AINSLIE MEARES
M.D., B.Agr.Sc. Melb., D.P.M.
OF MELBOURNE, AUSTRALIA

A SCHIZOPHRENIC patient is brought to us. We examine him, and we talk with the relatives. It must be a very common experience of all who are concerned with mental illness to look back and view the subtle changes which have taken place in the personality of the schizophrenic as his illness was developing. Unfortunately, we are usually aware of these changes only in retrospect. The thought must come to all of us—if only the patient had been brought to consultation earlier, we might have been able, by judicious psychotherapy and perhaps with adequate dosage of chlorpromazine, to ward off the illness without the development of psychosis, without the stigma of insanity, without loss of employment, and without any real disruption of home life.

What is needed is not the early diagnosis of schizophrenia but the diagnosis of prepsychotic schizophrenia. We must learn to recognise that state of mind which will develop into schizophrenia unless appropriate measures are taken to prevent deterioration. Clearly the recognition of this condition must depend on the general practitioner, for only through him will such patients be referred to the psychiatrist for assessment and treatment.

The Introvert and the Schizophrenic

Schizophrenia develops only in persons of introvert personality. If the apparent exceptions to this generalisation are studied in detail, they are usually found to be cases of pseudo-extroversion—i.e., people who have reacted to their introversion by overcompensation. They are distinguishable from the true extrovert by a certain incongruity of behaviour. Their apparent friendliness and ease of interpersonal relations is a little forced; it lacks real spontaneity, it does not ring true; and on psychological examination they disclose a subjective inner life which is quite unknown to the true extrovert.

Features of the introvert personality are sensitivity, subjectivity, active fantasy, idealism, and a need of privacy. The diagnosis of prepsychotic schizophrenia depends on the recognition of changes in the introvert personality towards the signs of schizophrenia—toward apathy, incongruity of affect, hallucinations, delusions, and impulsive acts. These changes can be recognised in the affect, thought, and behaviour.

Affect

Withdrawal

The introvert is essentially a highly sensitive person. Because he is so sensitive, he is often shy and ill at ease with his fellows. He is subject to imagined slights and insults. To save himself from the hurt of these situations, he defends himself by withdrawal. He does this by physically withdrawing and thus isolating himself, and also by withholding his emotions in his contacts with his fellows. This defence is characteristic of the introvert. It helps him to adjust to the reality of life situations with less anxiety. But trouble comes if the defence is pushed too far; he comes to isolate himself from his environment, and increasing withdrawal merges into the apathy of schizophrenia. We are thus confronted with the apparent paradox of the highly sensitive introvert becoming the apathetic schizophrenic.

In a similar way, the blunting of affect of the schizophrenic can be seen as a defence by the sensitive introvert against the too great disturbance of his emotions by experiences of little consequence. Blunting of affect is a dulling of emotional experience, and thus it serves to protect the introvert against his sensitivity.

For a period before the development of noticeable apathy, the patient goes through a phase of more and more complete withdrawal. This phase may extend over weeks, months, or years, according to whether the onset of the illness is acute, subacute, or insidious. In the adolescent or young adult, any change in behaviour towards greater withdrawal, or any lessening of emotional response, may be a sign of impending schizophrenic breakdown.

Anxiety

In most cases the patient suffering from schizophrenia in its fully developed form is relatively free from anxiety. Hence anxiety is often overlooked as an early sign of schizophrenia.

In a young introvert patient, anxiety for which no clear psychogenesis can be elicited should always lead the physician to suspect the possibility of prepsychotic schizophrenia. There are two main sources of such anxiety: it may come from a feeling of lack of unity in the self, a lack of psychic unison. The anxiety may be expressed as a sense of disintegration, or as a feeling of loss of contact with the outside world.

The patient with fully developed schizophrenia is usually unaware of the disintegration of his personality, but the prepsychotic schizophrenic may experience a very acute sense of disintegration. It seems that in the early stage of the illness the disharmony between thought and feeling may give rise to a sense of disintegration. These ideas are frequently given spontaneous expression if the prepsychotic schizophrenic is allowed to paint, or to model in clay. The feeling of disintegration is characteristically projected by making dismembered, eviscerated, or decerebrate figures. This may be at a time when the patient is still able to work and is still making a reasonable social adjustment.

The other common cause of anxiety in the prepsychotic schizophrenic concerns homosexual conflict. The repressive mechanism seems to be impaired by the developing psychosis, and repressed ideas of homosexuality come to consciousness. Very commonly the early schizophrenic of either sex, who has previously never been worried by this matter, expresses ideas of homosexuality. Clinically, this expression is accompanied by a much lower grade of anxiety than the acute panic which so often accompanies homosexual awareness in the true latent invert. In the prepsychotic phase, if the patient is allowed to express himself by graphic or plastic means, these ideas are often represented as bisexual symbols.

The prepsychotic schizophrenic is often able to control his anxiety so long as he is in a familiar environment, but in any unfamiliar situation his habitual defences function less effectively, and he manifests overt anxiety. In clinical practice, the easiest way of placing the patient in an

unfamiliar situation is to ask him to undress for physical examination. The prepsychotic schizophrenic often reacts with undue anxiety, and with a little judgment this anxiety may be used to elicit from him his sense of disintegration or homosexuality.

Inappropriate Emotional Response

Before the onset of that disharmony between thought and feeling which shows itself as incongruity of affect, there is often a phase of wistfulness. There is a faraway dreaminess, and a tendency to bemuse the self with the imponderable. The fleeting smile gives the impression that the patient has some understanding of matters which the observer does not experience.

This sign is very real, though hard to describe. It resembles the smile an adult might give when asked a naïve question by a child. The adult has understanding which the child cannot have. In a similar way the prepsychotic schizophrenic, because of his pseudophilosophical reverie, feels that he has some understanding which the physician cannot have.

Of course, a certain wistfulness is not abnormal in itself, but the change from a more outgoing type of emotional response to this kind of wistful behaviour may precede the development of a schizophrenic incongruity of affect.

This slight inappropriateness of emotional response may also be tinged with another quality. It may become a knowing smile, rather than an understanding smile; and as such it may spring from these seeds of suspicion which later develop into paranoid thinking.

An emotional disorder does not usually arise all of a sudden. Characteristically, there is a period in which a progressively less appropriate affect is displayed. Relatives and friends may be aware of a certain oddness about the patient, but this is so intangible that they rarely take heed of it. If it should come to the physician's notice, he must decide how long it has been present. A change in the nature of emotional response is much more significant than a slight inappropriateness in itself. Occasionally people of poorly integrated personality show an inappropriate affect, and so do those whose schizophrenia has been arrested at an early stage, either spontaneously or as a result of treatment. Compared with those suffering from overt schizophrenia, these people are relatively stable, and they are better regarded as having a schizophrenic character disorder. With them, a tendency to slightly inappropriate response is not to be taken as a sign of an active schizophrenic process.

Change of Mood

A change in the mood of the young introvert may be a danger signal. An alteration in the direction of mild euphoria is just as significant as a change towards melancholy. Because of his sensitivity and difficulty in making friends, the introvert is likely to suffer from a mild chronic depressive state. Those around him interpret any change to a happier disposition as an improvement. This may be so if the change is fairly gradual, when it probably results from some degree of maturation of his introvert personality. However, any rather sudden change to a happier disposition may well result from a greater activity of fantasy-life from increased introversion, and may be a sign that the manic type of onset of schizophrenia is impending. Points of diagnostic importance are that this happier state of mind is associated with greater withdrawal and isolation, and perhaps with some shift of interest from the practical to the more abstract; whereas the happier state of mind which results from maturation is associated with greater socialisation and firmer contact with reality.

If the change in mood is towards melancholy, there may be some self-depreciation. This is natural enough, because the introvert adjustment to life is less valued in Western culture than is extrovert adjustment. So this melancholy, coupled with self-depreciation, should not lead to the error of diagnosing an early depressive illness. The records of many chronic schizophrenics show that their first breakdown was diagnosed as hypomania, or as a depressive psychosis. The key to the situation is the person's basic introvert personality.

Thought

Symbolic Thinking

Schizophrenic patients often have a tendency to talk in riddles. This is a form of symbolic thinking. In the prepsychotic phase, an early sign of this tendency may be shown by the patient answering a question by himself asking a question. As he is still in reasonable contact with reality, his question is logical and relevant to the subject, but very characteristically it has a more abstract, a more philosophical, or a more mystical approach. The patient's question has the effect of reducing the reality value of the subject under discussion. For example, if the patient is asked about his trouble with his father, he may reply by asking some pseudophilosophical question about trouble.

Literal Thinking

The quality of thought of the prepsychotic schizophrenic is often very literal. There is a tendency to appreciate the meaning of words only in their literal sense. There is a failure to perceive any deeper meaning. This condition is tested by asking the patient the meaning of some well-known proverb. He offers a literal interpretation, and the deeper meaning tends to elude him. If he is asked the meaning of the expression " When the cat's away, the mice will play ", he may start by talking about cats and mice, and the real significance of the saying comes to him only later, or if suggested to him by the physician.

" Predelusional " Thinking

The prepsychotic schizophrenic characteristically shows evidence of predelusional thinking. This is most clearly exemplified by his ideas of reference, but these require very careful evaluation in each individual case.

Many shy, sensitive introverts experience fleeting ideas of reference. They are selfconscious. They feel that people are looking at them, or talking about them. Yet at the same time they retain a capacity to consider the matter realistically. They can pull themselves out of it, as it were—" It's silly of me to think like this; it's only that I'm too selfconscious." The ideas of reference can thus be banished more or less at will; and they do not become so compelling as to influence behaviour. This state of affairs is fairly common among sensitive introverts, and in itself is not evidence of impending psychosis.

But the time may come when there is a change in the nature of these ideas of reference, and the patient may be no longer able to dismiss them. At this stage he is likely to express his doubts to others, whereas earlier he took great care to keep his thoughts to himself. As the ideas of reference become more pressing, they influence his behaviour. He avoids a crowded street because he feels that people would talk about him. He overhears snatches of conversation, and misinterprets

them as referring to himself. Uncomplicated introversion has made the transition to prepsychotic schizophrenia.

Ideas of mission may be a significant sign of predelusional thinking; and in any young introvert such ideas call for careful evaluation. Idealism is a feature of the introvert personality; and young introverts are likely to become inspired with idealistic motives. The significant clinical feature concerns the reality content of such ideas. Thus an introvert student may say that he feels that he has a mission to help a certain underprivileged group of people. If we inquire about it, and he explains that he is going to qualify himself for the task in such-and-such a way, and then to set about it according to some realistic plan, his idea of mission has no pathological significance. On the other hand, if he is vague and diffuse, and tends to talk about Truth and Good in pseudophilosophical fashion, then we know that his ideas of mission have little contact with reality, and are significant signs of predelusional thinking.

Even if the ideas of mission seem well based on reality, it is wise to inquire about the source of inspiration. It may be that he has had some personal contact with, or has read about, the cause he proposes to embrace. On the other hand, it is well known that introverts who feel that they have had some personal revelation from God often become schizophrenic. In these circumstances, the point of diagnostic importance is the personal nature of the revelation; the person feels that he is singled out from all others. The feeling of being different is a precursor of the common grandiose delusions of the schizophrenic.

Somatic symptoms may have a delusional quality which can escape the most astute physician. In fully developed schizophrenia, they may have a bizarre quality which makes them easily recognisable as delusions. But in the prepsychotic stage there may be nothing unusual about the symptom itself: the diagnosis rests on the meaning of the symptom to the patient.

Sometimes we are given a clue by the odd way in which the patient presents his complaint:

A common example is the young introvert woman who complains of abdominal discomfort when there is no physical abnormality. She is reassured, and sent on her way. Then a few months later she openly expresses delusions of pregnancy, and the belief that she is about to bring forth the child of God.

In a similar way, the introvert youth may complain of vague lower-abdominal discomfort. Nothing abnormal is found on examination. He later develops schizophrenic ideas of homosexuality. In retrospect, we recognise that his symptoms were a projection of these feelings, and a request for the physician to examine his genitalia.

Devaluation of Reality

We have discussed the nature of the thought processes of the prepsychotic schizophrenic as symbolic, literal, and predelusional. If now we come to examine the actual thought content, we find that there is a consistent devaluation of reality. The introvert, with his subjectivity, his fantasy, and his idealism, is never a very down-to-earth practical type of person. He is more interested in abstract matters—in art, poetry, psychology, and philosophy—than in organising his life so as to make more money. An increase in this tendency to devalue reality may be a stage in the transition to a schizophrenic denial of reality.

The patient shows an increasing disregard of the practical aspects of day-to-day living. His job and his source of income seem to lose their significance. The provision of material comforts and necessities for himself and others is no longer important. In their place abstract considerations, such as Absolute Truth and the Meaning of Life, assume greater and greater importance, and occupy more and more of his time.

This process can sometimes be seen in changes of interest in subjects of study. The student may start with history, then change to psychology; but then he finds that parapsychology is his real interest, and he finally drifts into the study of metaphysics. The same process may sometimes be seen in medical students whose interest turns from surgery to internal medicine, and thence to psychiatry.

The devaluation of reality may show itself in a sudden interest in poetry and art. Modern poetry and modern art, rather than classical poetry and representational art, attract the prepsychotic schizophrenic. The relatively unstructured modern forms of expression allow the individual to fill in the gaps, as it were, with his own fantasy. We must be clear about this. I am not suggesting that all those whose interest turns to modern art are prepsychotic schizophrenics, but only that many introverts show a sudden preoccupation with these matters before a psychotic breakdown.

Revaluation of Basic Biological Events

The prepsychotic schizophrenic may sometimes be recognised by the way in which his thoughts become preoccupied with basic biological events such as birth and death. He ponders these matters, and revalues them so that they come to have a rather different meaning.

The young introvert woman may revalue the process of giving birth. It is the symbol of all creation. Compared with it, all other human activity pales into insignificance. She may talk a lot about birth to her friends or the local doctor, but not until a few months later, when she has achieved an extramarital pregnancy in foolish circumstances, is it recognised that her preoccupation was in fact an early sign of mental illness.

In a similar way, the prepsychotic schizophrenic may become preoccupied with the subject of death. This is quite distinct from the depressed patient who dwells on death because he feels hopeless or because he feels guilty, and believes that he is fit only for death. With the prepsychotic schizophrenic there is no self-accusation. He merely ponders the matter after the style of Hamlet. We may first become aware of the patient's state of mind because of some incident in which he has shown a disregard for his own safety. On talking with him it becomes clear that he was motivated neither by bravery nor by ideas of destruction, but merely by a disregard for death.

Revaluation of Religious and Political Beliefs

There is a tendency for the prepsychotic schizophrenic to revalue his traditional religious and political beliefs. The uncertainty about himself, which arises from lack of cohesion of the elements of his personality, is projected on to the world around him. He becomes unsure of the beliefs on which he has been reared.

The Protestant youth may feel a greater security in the dogma of the Catholic Church. The Catholic youth in his turn feels that his Church does nothing to alleviate his inner disquiet, so he abandons religion for atheism. In either case, the change results from disturbing influences within the individual's own psyche, rather than from real religious experience. Similar signs may be seen in a revaluation of political beliefs. The youth brought up in a Conservative household may suddenly turn Communist, or vice versa.

Of course, many people in normal health experience religious conversion or change of political belief; but in a young introvert such changes should be regarded as possible signs of prepsychotic schizophrenia, and should lead the physician to a close examination of other facets of the individual's personality.

Behaviour

Increased Introversion

As a rule, the young introvert who is losing his hold on reality does not tell people about his difficulties. For the most part, it is only through his behaviour that those around him learn that all is not well.

As would be expected, any manifestation of increased introversion may be a sign of impending psychosis. There may be increased withdrawal from the companionship of others, a greater tendency to isolation, a desire to be by himself, long periods spent in his room alone in which he neither reads nor listens to the radio but just sits in silence.

There may be signs of regression. The lad of 20 may revert to a more childish pattern of behaviour. He is careless of his appearance, and becomes less fastidious about his personal cleanliness. He is untidy and inattentive. He lacks concentration, and there is a falling off in his work record.

The patient with fully developed schizophrenia often masturbates quite openly. Masturbation is a common problem of the shy, sensitive introvert. In the prepsychotic phase of his illness there may be lapses of social propriety in which he may absentmindedly masturbate in the presence of others; or he may no longer conceal the fact that he has masturbated.

Decreased Introversion

Though less widely recognised, an apparent decrease of introversion may be an unmistakable warning of impending schizophrenia. The diagnostic features of such a decrease of introversion are that it is sudden and incongruous.

The introvert who is making progress towards maturity shows a decrease of introversion. But this is always a slow process; the changes come gradually, and they are well based on reality concepts and easier interpersonal relationships. On the other hand, the decrease of introversion which is of bad import comes suddenly and unexpectedly. The shy, timid youth suddenly starts asking out girls whom he hardly knows. If questioned about it, he rationalises that his friends do likewise. But there is an essential incongruity in the situation. It is really not so much a decrease in introversion as that his judgment is astray; he is losing his hold on reality.

The condition may manifest itself in numerous ways. The boy who has been habitually reserved at parties suddenly loses his shyness. He talks loudly, slaps people on the back, and drinks much more than is his custom. This reaction is distinguished from the compensatory pseudo-extrovert behaviour of some introverts by its sudden development, and the fact that it is contrary to the individual's habitual pattern of behaviour.

Lack of Propriety

There is often a lack of propriety about the behaviour of the prepsychotic introvert. This is difficult to define. The patient's behaviour may be normal enough in itself, but inappropriate. The young woman loses her sense of dress. Individual items of her dress may not harmonise, or it may be unsuitable to the occasion. Again, there may be an inappropriate response to the niceties of social circumstances. Jokes may be told which are not fitting in the circumstances. A youth may come into the consulting-room smoking, when his background suggests that he should be better-mannered.

Fads and Mannerisms

The development of food fads or mannerisms may be an early sign of prepsychotic schizophrenia. These abnormalities of behaviour seem to have some deep meaning or symbolic significance.

The patient may suddenly refuse to eat meat. He usually rationalises by saying that it disagrees with him, or that he is allergic to it. At a deeper level, it is related to his introvert idealism; so that he feels he must not live by the slaughter of other creatures.

Common mannerisms are the continual touching of the mouth with the fingers, pulling the ear, or running the fingers through the hair. These are distinguished from obsessive-compulsive phenomena on the one hand, and hysterical tics on the other, by the basic personality of the individual. We must remember that, by virtue of their symbolic significance, these fads and mannerisms may acquire a protective value to the patient, so that an attempt at forcible control may precipitate frank psychosis. A young introvert woman who had taken to wearing a black patch over one eye developed a psychosis when the patch was removed by an ophthalmologist; however, the psychotic symptoms ceased when the eye was again covered.

Evaluation of Signs

The diagnosis of prepsychotic schizophrenia requires more than the recognition of these signs in the individual's affect, thought, and behaviour. It requires their careful evaluation. Change in the magnitude of a particular sign is of greater significance than the sign itself.

Any sign must be considered in relation to other facets of the individual's personality. We must decide whether or not the sign has some special meaning to the patient, or shows a less firm contact with reality, and thus indicates an increase of introversion.

The regular diagnosis of schizophrenia before the actual signs of psychosis develop must surely be our first step towards reducing the toll of this scourge of humanity.

Summary

Prepsychotic schizophrenia is diagnosed by recognising changes in the affect, thought, and behaviour of the person of introvert personality. Greater withdrawal, unexplained anxiety, inappropriate emotional responses, and changes in mood, either towards depression or towards euphoria, may be danger signs. There may be evidence of symbolic or literal thinking. Queer bodily symptoms may precede somatic delusions; and ideas of reference or ideas of mission may be signs of impending paranoid thinking. Before the advent of frank psychosis there is often a devaluation of reality, and a revaluation of basic biological events. The patient's behaviour suggests increased introversion. A sudden apparent decrease of introversion usually indicates a less firm contact with reality. The patient may show a subtle lack of propriety, as well as various fads and mannerisms. The significance of any sign must be evaluated with reference to other aspects of the patient's personality.

REFERENCE

Meares, A. (1958) The Introvert. Springfield, Ill.

THE CHOICE BETWEEN DEATH FROM POSTMATURITY OR PROLAPSED CORD AND LIFE FROM INDUCTION OF LABOUR

G. W. THEOBALD
M.A., M.D. Cantab., M.R.C.P., F.R.C.S.E., F.R.C.O.G.
From St. Luke's Maternity Hospital, Bradford

LONDON obstetricians agreed in 1756 on the moral rectitude of and the therapeutic advantages which might follow the induction of premature labour in multigravidæ with minor pelvic contraction. This has remained a largely English procedure, because Sigault in 1777 successfully performed symphysiotomy for contracted pelvis, and his operation found greater favour with Continental obstetricians.

The commonest modern indication for the induction of labour is suspected placental deficiency, associated either with so-called pregnancy toxæmia or with postmaturity. There is, however, a revival of induction of labour for minor cephalopelvic disproportion, and not only in multigravidæ (Drew Smythe 1949, Tennent and Black 1954, MacLennan 1954).

The consultant staff of St. Luke's Maternity Hospital, Mr. G. A. Craig, Mr. A. C. Muir, and myself, meet each month and agree in detail on hospital policy, particularly as it affects registrars and nursing staff, thus leaving latitude for the treatment of individual patients by each consultant. Weekly antenatal care and induction of labour are regarded as the main instruments of hospital policy.

Believing that the risks associated with induction of labour are related more to the stage of pregnancy than to the reason for the operation, the patients have been divided into those induced before the 38th week, those between the 39th and 40th weeks, and those after the end of the 40th week of pregnancy. Adequate antenatal care should make it unnecessary, except in structurally defective women, to induce labour before the 38th week, and most of the cases reported here were emergency admissions. The figures have, moreover, been analysed to show the numbers of gravida 1, gravida 2 and 3, and gravida 4 and more, in each group. Pregnancies of less than 28 weeks have been disregarded.

Indications for Induction of Labour

Hypertension

The standard adopted is at least two readings of or above 140/90 mm. Hg before the onset of labour. For some years we allowed patients with uncomplicated hypertension to proceed to term, but we now tend to induce them between the 38th and 40th weeks, providing the cervix is reasonably ripe. The perinatal mortality in this group has remained constant at between 5% and 6%, and no differentiation is made between "essential" hypertension and that arising during pregnancy. This change in policy was largely forced on us by shortage of antenatal beds.

Hypertension + Proteinuria

The perinatal mortality has remained constant in this group (H+P) at about 20%. The majority of inductions of labour before the 38th week were in this group, and most of the patients were emergency admissions.

High Head

Perhaps some of the most rewarding reasons for induction of labour, notwithstanding the observations of Gibson (1952) and Parker (1957), are included in table I under the heading of "free head+". This includes minor degrees of cephalopelvic disproportion, oblique lie, high presenting part, previous cæsarean section, and all conditions in which it is possible for a limb or the cord to prolapse. Recent reports have stressed both the maternal and fœtal dangers associated with the confinement of grande multiparæ in unsuitable surroundings. They are often unwilling and indeed unable to come into hospital because they cannot leave their children. We are willing to admit them at the weekend for induction of labour so that their husbands can look after the children. They are allowed home, if all proceeds normally, within 48 hours of delivery.

Postmaturity

The most disputed indication for induction is postmaturity. Ballantyne and Browne (1922) recognised the "undoubted" dangers of postmaturity both to mother and child, which they thought to be almost entirely due to the large size of the infant. They therefore advocated induction of labour soon after term. Hamilton (1949), Racker et al. (1953), Clifford (1954), Tennent and Black (1954), Gibson (1955), Strand (1956), Lindell (1956), and Blaikley (1956), among others, believe that prolongation of the pregnancy is associated with increased fœtal mortality, whereas Calkins (1954), Burnett (1955), Hill (1952), Daichman and Gold (1954), Evans (1954), Clayton (1941), Browne (1957), and Macafee and Bancroft-Livingston (1958) are among those who either hold the contrary view or doubt the wisdom of inducing labour.

Greenhill (1954-55) believes that few obstetricians in the United States regard postmaturity as a serious problem. On the other hand, some American pædiatricians

TABLE I—METHODS OF DELIVERY AND REASONS FOR INDUCING LABOUR (GROUP 2: WOMEN 38 TO 40 WEEKS PREGNANT)

—	Total	No. of cases of										
		Spontaneous delivery	Oxytocin drip	Cæsarean section	Forceps	Hypertension alone	H+P	H+O	H+P+O	A.P.H.	Rhesus antibodies	Free head+
Primigravidæ ..	109	74 (68·0%)	30 (27·5%)	7 (6·4%)	28 (26·0%)	52 (48·0%)	18 (16·5%)	14 (12·8%)	4 (3·7%)	6 (5·5%)	1 (0·9%)	8 (7·3%)
Grav. 2 and 3 ..	148	137 (92·5%)	29 (19·6%)	8 (5·4%) (5 repeat)	3 (2·0%)	61 (41·2%)	13 (8·8%)	6 (4·0%)	3 (2·0%)	8 (5·4%)	10 (6·8%)	36 (24·3%)
Grav. 4 and + ..	49	48 (98·0%)	12 (24·0%)	1 (2·0%)	1 (2·0%)	12 (24·0%)	2 (4·0%)	1 (2·0%)	0	5 (10·0%)	5 (10·0%)	12 (24·0%)
Totals	306	259 (84·6%)	71 (23·2%)	16 (5·3%)	32 (10·5%)	125 (40·8%)	33 (10·8%)	21 (6·9%)	7 (2·3%)	19 (6·2%)	16 (5·3%)	56 (18·3%)

H+P = hypertension together with proteinuria; H+O = hypertension together with œdema; H+P+O = hypertension associated with both proteinuria and œdema; A.P.H. = antepartum hæmorrhage. "Free head +" embraces cephalopelvic disproportion, previous cæsarean section, oblique lie, and high head.

write of a postmaturity syndrome, and Clifford (1954) affirms that " postmaturity ranks second only to prematurity as a cause of fœtal and neonatal mortality in primiparous women ".

Whereas Browne and Veall (1953), Morris et al. (1955, 1956), and Johnson and Clayton (1955) have shown that hypertension is associated with a diminished blood-supply to the uterus and placenta, no evidence has been produced to show that uncomplicated postmaturity is accompanied by a progressive diminution in the blood-supply to these structures.

Walker and Turnbull (1953) and Turnbull and Walker (1955) have attributed the increased perinatal mortality after the 41st week to fœtal anoxia, a view which has largely been substantiated by MacKay (1957). Bancroft-Livingston and Neill (1957), however, have recently challenged these findings, for they were unable to find any correlation between the oxygen level of umbilical venous blood and either fœtal or maternal age.

There is no general agreement on the incidence of postmaturity. Nesbitt (1957) states that from 10% to 12% of pregnancies extend to or beyond the 294th day, and that 3%–4% exceed 300 days. He found that the incidence of postmaturity varied with race, parity, and age, and was greater in non-white than white and in primigravidæ than in multigravidæ, notably in elderly primigravidæ. Macafee and Bancroft-Livingston (1958) quote figures varying from 2·6% to 13·5%, and whereas their own incidence was 7·7%, the senior author noted it in only 2·9% of his private patients. Gibberd (1958) gives the very high figure of 31%, of which only 4·8% carried beyond the 42nd week.

In just over 3500 cases reported by general practitioners (College of General Practitioners 1957) the incidence of postmaturity exceeding 42 weeks was 2·5%. Our own incidence was 12%, but this figure is of no great significance for two reasons: (1) between 15% and 20% of all our deliveries are emergencies; and (2) we induce labour as soon as possible after the 292nd day of pregnancy.

Figures for perinatal mortality due to postmaturity vary from 1·1% (Gibberd 1958) to 8·7% (Racker et al. 1953). While expressing no opinion as to the cause of this mortality, it may be observed that the fœtus does not live by oxygen alone, that incoordinate uterine activity and oligohydramnios may be significantly involved, and that there is no justification for so wide a divergence in the figures.

Gibberd (1958), for example, excludes all fœtal deaths which he does not attribute to anoxia, and then by including women 41 and 42 weeks pregnant arrives at the irrelevant figure of 1·1% for fœtal loss due to postmaturity. Obstetricians who are most conscious of the risks of prolonged pregnancy do not induce labour because of it until towards the end of the 42nd week, and Gibberd's figure should therefore be approximately 3·2%. A conservative estimate for hospital practice in this country would be 4%, which lies between the corrected figures of Gibberd (1958), and Macafee and Bancroft-Livingston (1958).

So heavy a perinatal mortality cannot be contemplated with equanimity today, for the main risks to the fœtus (prematurity, toxæmia, antepartum hæmorrhage, and fœtal abnormalities) should be safely past by the end of the 41st week of pregnancy. The postmature infant has merely to survive the hazards of birth, whereas to the premature infant, extrauterine existence poses almost as great a challenge. It is reasonable to go further and postulate that stillbirths due to accidental hæmorrhage, eclampsia, prolapse of the cord, and like conditions, which arise after the 42nd week, should be attributed to postmaturity. Postmaturity, like prematurity, probably varies not only with race and age, but also with the social grade of the patient, and provides the largest single presently preventable source of fœtal loss.

To make this point crystal clear, let it be stated that of the 70 stillbirths during 1957 amongst 2095 booked patients, 63% weighed less than 4 lb. (1·8 kg.), 79% were premature, and only 15 (21%) weighed over 5½ lb. (2·5 kg.). Of these 15, 6 had malformations incompatible with life, and 4 died in utero before admission, for no discoverable reason. Of the 35 neonatal deaths in the same group, 57% were premature and 31% weighed less than 4 lb. (1·8 kg.). Only 15 infants weighed more than 5 lb. 8 oz. (2·5 kg.), and of these 7 had serious congenital malformations which caused death, and 1, delivered into a bucket by a mentally defective patient, died shortly after admission. During the whole year, therefore, only 12 " mature " perinatal deaths might have been avoided. It is in this conjunction that a potential loss of 4% of babies more than 2 weeks postmature assumes a new significance, particularly in industrial cities with a high proportion of citizens belonging to the lowest social grades.

The Induction

Amniotomy is performed in the obstetric theatre, not in a labour ward, and by a consultant or registrar, and not by a house-surgeon. The patient is given 100 mg. of pethidine and 25 mg. of chlorpromazine, either intramuscularly about an hour before or intravenously just prior to the operation. Alternatively, she is allowed to give herself trichlorethylene through a standard machine.

She is placed in the lithotomy position, with the table in the Trendelenburg position. The most scrupulous antiseptic and aseptic precautions are taken. The half-hand is then introduced into the vagina, which is literally filled with obstetric cream, and the finger or fingers which are introduced through the ripe cervix * separate the membranes from the lower uterine segment as far as possible. The membranes are ruptured in the most dependent part with an ordinary catheter stilette. The hole is then widely enlarged and as much liquor amnii as possible is allowed to drain away. It may take ten minutes for this to happen and during the whole of this time the flow is controlled by the finger or fingers in the cervix, which are not removed until the operation is complete. The presenting part must be safely housed over the pelvic brim and " gripped " by the lower uterine segment before the patient is returned to the ward, and it may sometimes be desirable to inject 1 or 2 units of oxytocin intramuscularly to further this aim.

On her return to bed she is given 2 oz. of castor oil, followed some three hours later by a copious warm enema. Some feel that it is no longer necessary to give so unpleasant a purgative and they may be right. Castor oil, however, is the only purgative in general use that acts on the small as well as the large gut, and it remains to be proved that equally successful results can be obtained without it. It is probable that the vomiting it sometimes causes is as likely as purgation to stimulate the hypothalamus.

We give all mothers 10 mg. of vitamin K orally every 8 hours from the time of amniotomy until delivery is complete. We have also given, in the interests of the infant, 500,000 units of penicillin twice daily from the time the membranes have been ruptured until delivery is complete. More recently a sulphonamide has been used by one of my colleagues, and in

* " Ripe cervix " is a horticultural term used in an almost riparian setting which denotes a soft cervix which is taken up and admits one or two fingers. I prefer not to induce labour in a primigravida if the cervix is not ripe, and entertain some doubts concerning grossly fat women with short necks, thick dry skin, and other evidence of possible endocrine disorder. Those who disregard the ripeness of the cervix use as their criterion whether the woman goes into labour within 72 hours, whereas mine is whether she goes into labour within 12 hours.

many cases the penicillin has not been given until the membranes have been ruptured for 12 hours. It may not be very logical to give penicillin, because bacilli of the coli group are likely to be involved; but the organisms which affect the respiratory system of the infant may be sensitive to penicillin. The fact remains that it came into use long before the broad-spectra antibiotics were available and has worked very satisfactorily. I would not advocate the routine use of the newer antibiotics, neither have I the courage to assert that no prophylactic treatment is necessary. In a very few cases, when the period from amniotomy to delivery is prolonged, we give tetracycline both to the mother and her infant.

The Physiological Oxytocin Drip

If the patient is not in labour on the morning following amniotomy, the oxytocin drip is usually started.

½ unit of oxytocin is added to the drip bottle, containing 540 ml. of 5% glucose in distilled water. A label is immediately fixed to the bottle, upside down. It is convenient to add 1 unit to another bottle and label it. We have increasingly used the synthetic preparation, ' Syntocinon ', for the simple reason that it can be obtained in ampoules containing 2 units in 2 ml. Using a tuberculin syringe, the house-surgeon can add either 0·5 or 1 ml. of this preparation to the bottle, whereas ' Pitocin ', which is equally efficient, needs previous dilution before it can be added to the glucose solution.

A no. 2 hypodermic needle, which requires an adapter to connect with the giving-set, is introduced into a vein over the wrist. This allows considerable movement of the arm. The house-surgeon stays with the patient for half an hour and then the nursing staff take charge. The pulse and fœtal heart are counted hourly, as in all other patients in labour, and the blood-pressure and temperature are taken four-hourly. If the patient is hypertensive the blood-pressure is recorded hourly. 1 unit of oxytocin, added to the bottle and delivered at the rate of 40 drops a minute, is regarded as the extreme range of the physiological oxytocin drip, and we never use more than 2 units in the bottle, which I arbitrarily regard as pharmacological. We believe in deep sedation and besides giving morphine, pethidine, and chlorpromazine freely by the intramuscular route, we often add them to the drip bottle. The drip is always taken down in the evening unless delivery is imminent.

Results

The fact that the number of inductions of labour has increased from 306 in 1952 to 666 in 1957, making a total of 2631 for the 6 years, indicates satisfaction with the procedure. These figures include both booked and unbooked patients. The results of the 1030 cases induced between 1952 and 1954 inclusive, were reported by Theobald, Kelsey, and Muirhead (1956).

There was only 1 maternal death amongst the 2631 patients in whom labour was induced. It was due to air embolism and was in no way related to the induction of labour.

During 1957, 2734 women gave birth to 2793 infants. An induction card is completed for every patient in whom labour is induced, and a separate card is filled in if an oxytocin drip is used. Labour was induced in 666 patients (24% of all deliveries), but this figure does not include 50 inductions because of anencephaly, hydrocephaly, or death of the fœtus. It seems unreasonable to include these in a review concerned with the safety of induction of labour. Moreover amniotomy was performed on a further 287 patients, either because labour had not started after spontaneous rupture of the membranes, or because of its unsatisfactory progress.

The patients have been divided into four groups: (1) those induced before the 38th week; (3) those induced between the 38th and 40th weeks; (4) postmature women; and (4) all induced patients who were given an oxytocin drip.

GROUP 1: INDUCTION BEFORE 38 WEEKS
(26 cases [4%,] perinatal mortality 2 [8%])

Induction of premature labour before the 38th week was performed in only 26 cases, nearly all emergencies. The smallness of this group proves that the virtual elimination of eclampsia, and the halving of the number of cases of hypertension associated with proteinuria (over a period of ten years) has not been achieved by frequent resort to the induction of premature labour.

The indication for induction in this group was what would elsewhere be called severe pre-eclampsia. The 2 infant deaths were associated with accidential hæmorrhage, and both children weighed under 4 lb. (1·8 kg.). No further reference will be made to this small group (although a few are included in table VI).

GROUP 2: INDUCTION BETWEEN 38 AND 40 WEEKS
(306 cases [46%], perinatal mortality 7 [2·5%], corrected perinatal mortality 4 [1·3%])

The reasons for induction of labour and the results obtained are shown in table I. Hypertension, either by itself or associated with proteinuria (H+P), or œdema (H+O), or with both proteinuria and œdema (H+P+O), was by far the commonest indication (88%). The 109 primigravidæ in this group included a high proportion of the patients in whom difficulties were encountered. Only 68% delivered themselves spontaneously; 28% required an oxytocin drip, 6% were delivered by cæsarean section, and 26% by forceps.

The last column, " free head+", includes cephalopelvic disproportion, previous cæsarean section, oblique lie, and high head, and therefore some of the most difficult cases. It was the indication for induction in 7% of the primigravidæ and in nearly a quarter of the multigravidæ. 5 repeat cæsarean sections were performed because of cephalopelvic disproportion in the gravida-2 and -3 group.

GROUP 3: POSTMATURITY
(334 cases [50%], perinatal mortality 1 [0·3%])

Although some of these patients had hypertension, the main indication for terminating pregnancy was postmaturity (table IA). Term is calculated by adding 7 days from the first day of the last menstrual period and counting back 3 months. Term+10 days is the indication for induction. Nearly all of these patients delivered themselves spontaneously; the cæsarean-section rate was 1·5%, and the forceps-rate only 3·8%.

TABLE IA—METHODS OF DELIVERY (GROUP 3: POSTMATURE WOMEN)

	Total	No. of cases of			
		Spontaneous delivery	Oxytocin drip	Cæsarean section	Forceps
Primigravidæ	150	133 (88·0%)	29 (19·3%)	4 (2·7%)	13 (8·7%)
Grav. 2 and 3	125	124 (99·0%)	6 (4·0%)	1 (0·9%)	1 (0·9%)
Grav. 4 and +	59	59 (100%)	10 (17·0%)	0	0
Totals	334	316 (95·0%)	45 (13·5%)	5 (1·5%)	14 (3·8%)

Maternal Age

The effect of age is shown in table II. It is interesting that 24% of the primigravidæ in group 1, and 26% in group 3, were 30 years of age or over, whereas the corresponding figure in the postmaturity group was only 15%. This same trend is seen in the gravida-2 and -3

TABLE II—MATERNAL AGE-DISTRIBUTION IN GROUPS 2, 3, AND 4

	Group 2: Women 38–40 weeks pregnant						
	−20 years	20–24 years	25–29 years	30–34 years	35–39 years	40+ years	Total
Primigravidæ ..	16 (15%)	43 (39%)	24 (22%)	16 (15%)	9 (8%)	1 (1%)	109
Grav. 2 and 3 ..	2 (1%)	34 (23%)	48 (32%)	39 (26%)	23 (16%)	1 (1%)	147
Grav. 4 and + ..	0	4 (8%)	8 (16%)	12 (25%)	18 (37%)	7 (14%)	49
	Group 3: Postmature women						
Primigravidæ ..	27 (18%)	65 (44%)	35 (24%)	19 (12%)	4 (3%)	0	150
Grav. 2 and 3 ..	5 (4%)	44 (35%)	44 (35%)	19 (15%)	10 (8%)	2 (2%)	124
Grav. 4 and + ..	0	1 (2%)	14 (24%)	20 (34%)	16 (27%)	8 (14%)	59
	Group 4: Women given an oxytocin drip						
Primigravidæ ..	7 (11%)	20 (32%)	18 (29%)	8 (13%)	8 (13%)	0	61
Grav. 2 and 3 ..	0	11 (23%)	18 (37%)	11 (23%)	7 (14%)	2 (4%)	49
Grav. 4 and + ..	0	3 (9%)	7 (22%)	6 (19%)	11 (34%)	5 (16%)	32

sections, where the comparable figures are 43%, 41%, and 25% respectively. A higher than average proportion of elderly primigravidæ is to be found among patients with hypertension, and an oxytocin drip is more often necessary in the older age-groups. The age-distributions in these groups can be compared with those for the whole hospital which are shown in table III.

Weight of Baby

It is very desirable to have reliable evidence of the duration of pregnancy before inducing labour for postmaturity, and the only infant lost in this group died from atelectasis, was born to an unbooked patient, and was not postmature. The ideal evidence is a note concerning the size of the uterus made at vaginal examination at about the 12th week. Nevertheless it is satisfactory that, notwithstanding the fact that 6% of babies born to primigravidæ weighed less than 6 lb. (2·7 kg.), 79% weighed over 7 lb. (3·2 kg.) (table IV). This figure compares with 55% in group 1, and 51% in group 3, and is independent evidence that the concept of postmaturity is a real one. The unsatisfactory suggestion that some babies take longer to mature than others may, therefore, be discarded. It is quite clear that the weight of the baby plays little or no part in determining the necessity for an oxytocin drip.

Speed of delivery

Table V shows that of the 523 patients who did not have an oxytocin drip, 91% were delivered within 24 hours of amniotomy, 80% within 18 hours, 61% within 12 hours, and 18% within 6 hours of rupture of their membranes. The figures for the primigravidæ show, rather surprisingly, that 81% of those in group 2, and 93% in group 3, were delivered within 24 hours of amniotomy.

GROUP 4: OXYTOCIN DRIP

The most revealing table, table VI, shows, when compared with tables I and IA, that nearly all the cæsarean sections (4 were from group 1), and 70% of the forceps deliveries were in this small group of 142, which included a high proportion of elderly patients. But the obstetric difficulties were not reflected in perinatal mortality. Other features in table VI are:

(1) Although 34% of all patients took more than 24 hours to achieve delivery after the drip was set up, in only 12% was it used on more than 2 days.

TABLE III—MATERNAL AGE: OVERALL HOSPITAL DISTRIBUTION, 1957

—	Total	No. of women in different age-groups						No. of women aged 30 and over
		Under 20	20–24	25–29	30–34	35–39	40 and +	
Primigravidæ	1194	206 (17%)	469 (36%)	305 (26%)	147 (12%)	54 (5%)	13 (1%)	214 (18%)
Grav. 2 and 3	1045	32 (3%)	258 (25%)	344 (33%)	263 (25%)	114 (11%)	34 (3%)	411 (39%)
Grav. 4 and +	497	0	35 (7%)	120 (24%)	134 (27%)	158 (32%)	50 (10%)	342 (69%)

TABLE IV—WEIGHT OF BABIES IN GROUPS 2, 3, AND 4

	10 lb. and over (4·6 kg.)	Between 9 and 10 lb. (4·1–4·6 kg.)	Between 8 and 9 lb. (3·64–4·1 kg.)	Between 7 and 8 lb. (3·2–3·6 kg.)	Between 6 and 7 lb. (2·7–3·2 kg.)	Between 5 and 6 lb. (2·3–2·7 kg.)	Between 4 and 5 lb. (1·8–2·3 kg.)	Between 3 and 4 lb. (1·4–1·8 kg.)
	Group 2: Women 38–40 weeks pregnant							
Primigravidæ ..	1 (1%)	2 (2%)	15 (14%)	41 (38%)	36 (33%)	12 (11%)	1 (1%)	1 (1%)
Grav. 2 and 3 ..	1 (1%)	4 (3%)	28 (19%)	46 (31%)	44 (30%)	21 (14%)	3 (2%)	0
Grav. 4 and + ..	0	4 (8%)	7 (14%)	14 (29%)	17 (35%)	4 (8%)	3 (6%)	0
	Group 3: Postmature women							
Primigravidæ ..	0	6 (4%)	27 (18%)	86 (57%)	23 (15%)	7 (5%)	1 (1%)	0
Grav. 2 and 3 ..	1 (1%)	7 (6%)	28 (23%)	47 (39%)	32 (26%)	6 (5%)	0	0
Grav. 4 and + ..	2 (4%)	7 (12%)	10 (18%)	20 (35%)	12 (21%)	6 (11%)	0	0
	Group 4: Women who received an oxytocin drip							
Primigravidæ ..	0	0	14 (23%)	17 (28%)	19 (31%)	10 (16%)	0	1 (2%)
Grav. 2 and 3 ..	1 (2%)	2 (4%)	7 (15%)	11 (23%)	22 (46%)	5 (10%)	0	0
Grav. 4 and + ..	0	0	9 (28%)	8 (25%)	11 (34%)	4 (13%)	0	0

TABLE V—HOURS FROM AMNIOTOMY TO DELIVERY IN PATIENTS WHO DID NOT REQUIRE AN OXYTOCIN DRIP

	Total	6 hours or less	7 to 10	11 to 12	13 to 18	19 to 24	25 to 36	36+
	Group 2: Women 38–40 weeks pregnant							
Primigravidæ ..	80	10 (12·5%)	14 (17·5%)	12 (15·0%)	16 (20·0%)	13 (16·3%)	14 (17·5%)	1 (1·2%)
Grav. 2 and 3 ..	110	27 (24·6%)	28 (25·5%)	14 (12·7%)	21 (19·1%)	12 (10·9%)	6 (5·5%)	2 (1·8%)
Grav. 4 and + ..	43	6 (14·0%)	10 (23·2%)	12 (28·0%)	8 (18·6%)	4 (9·3%)	3 (7·0%)	0
	Group 3: Postmature women							
Primigravidæ ..	122	10 (8·2%)	41 (33·6%)	14 (11·5%)	33 (27·0%)	15 (12·3%)	8 (6·6%)	1 (0·8%)
Grav. 2 and 3 ..	118	27 (22·9%)	48 (40·7%)	12 (10·2%)	13 (11·0%)	11 (9·3%)	7 (5·9%)	0
Grav. 4 and + ..	50	15 (30·0%)	16 (32·0%)	4 (8·0%)	6 (12·0%)	3 (6·0%)	4 (8·0%)	2 (4·0%)
Totals	523	95 (18·2%)	157 (30·0%)	68 (13·0%)	97 (18·7%)	58 (11·2%)	42 (8·4%)	6 (1·1%)

(2) 25% of patients required only ½ unit of oxytocin, and 61% 1 unit added to the drip bottle.

(3) Only 14% (20 patients) out of the 666 induced required a drip containing more than 1 unit of oxytocin in the bottle.

SUMMARY OF RESULTS IN THE 640 PATIENTS IN GROUPS 2 AND 3

Perinatal mortality.—The total uncorrected perinatal mortality was 8 (1·3%). Of these, 3 had malformations incompatible with life; 1 was associated with accidental hæmorrhage, and 1 with placenta prævia; only 3 babies were lost to mothers in whom elective induction of labour was performed—a perinatal mortality of 0·5%.

Incidence of cæsarean section.—Groups 2 and 3, 3·3% (group 3, 1·5%); compared with an overall hospital incidence of 3·3% and a Bradford city incidence of under 2%.

Incidence of forceps delivery.—Groups 2 and 3, 7% (group 3, 3·8%); compared with an overall hospital incidence of 8·5% and an incidence in booked patients of 6·4%.

Of 2132 babies delivered to booked mothers only 2 weighing over 4 lb. (1·8 kg.) died because of, or in association with, prolapse of the cord.

Only 11 of the 2095 booked patients had labours lasting more than 48 hours. During 1957 amniotomy was performed just over 1000 times, or in 37% of all deliveries. It was done to induce labour in 24% of all deliveries.

Discussion

There is general agreement that surgical induction of labour is now safe for the mother, although Parker (1957) reported 4 maternal deaths among 1099 women in whom labour was induced. It is impossible to compare the perinatal mortality figures following this operation in different centres: they vary from an uncorrected figure of 9·1% (Parker 1957) to a corrected 1·6% (Lennon 1957). Moreover, terms are used in such a way that they confuse rather than enlighten. Cope and Pearson (1958), for example, admitted that most of their cases of hypertension and pre-eclampsia were "mild", and many of them would not have even been considered hypertensive at other centres. Further, it is obvious that such terms as minor degrees of contracted pelvis and cephalopelvic disproportion are valid only in the minds of the obstetricians concerned, and results cannot be directly compared. When induction of labour is carried out for urgent and imperative reasons, such as true pre-eclampsia and toxæmic accidental hæmorrhage, and before the 38th week, the perinatal mortality will usually be high. Such cases, together with those of placenta prævia and those in which the fœtus is known to be dead, should properly be excluded from a review concerned with the merits of the procedure itself.

For this reason postmaturity provides the best standard for assessing its worth. Tennent and Black (1954) reported for this group a corrected perinatal mortality of 1%, Parker (1957) 2%, Gibberd (1958) 6%, and our figure is 0·3%. Turnbull and Baird (1957) have also achieved outstanding results; but they have not hesitated to resort freely to cæsarean section, particularly in primigravidæ aged 25 or over.

One other measurement of efficiency can be applied, the number of times the cord prolapses during or after amniotomy: Gibson (1952) 1 in 731; Tennent and Black (1954) 1 in 1585; Parker (1957) 11 in 1099 (1%); Evans (1954) 16 in 507 amniotomies (3·7%). It is thus

TABLE VI—WOMEN GIVEN AN OXYTOCIN DRIP (GROUP 4)

	Total	No. of cæsarean sections*	No. of forceps	Hours from induction to drip				Hours from drip to delivery					Concentration of drip			Days used			
				12 and less	13 to 24	25 to 36	36+	6 and less	7 to 12	13 to 24	25 to 36	36+	½ unit	1 unit	2 units	1	2	3	4
Primigravidæ	62	8 (13%)	21 (34%)	14 (23%)	37 (60%)	7 (11%)	4 (7%)	15 (24%)	13 (21%)	4 (6·5%)	15 (24%)	15 (24%)	12 (19%)	38 (61%)	12 (19%)	42 (68%)	8 (13%)	12 (19%)	0
Grav. 2 & 3	48	10 (20%)	10 (21%)	10 (20·8%)	27 (56%)	8 (17%)	3 (6%)	11 (23%)	12 (25%)	15 (31%)	4 (8%)	6 (12%)	14 (29%)	28 (58%)	6 (12%)	38 (79%)	7 (15%)	1 (2%)	2 (4%)
Grav. 4 and +	32	4 (12·5%)	1 (3%)	7 (22%)	20 (63%)	4 (13%)	1 (3%)	12 (38%)	8 (25%)	4 (13%)	4 (13%)	4 (13%)	9 (28%)	21 (66%)	2 (6%)	24 (75%)	6 (19%)	2 (6%)	0
Total	142	22 (15·5%)	32 (22·5%)	31 (22%)	84 (59%)	19 (13%)	8 (6%)	38 (27%)	33 (23%)	23 (16%)	23 (16%)	25 (18%)	35 (25%)	87 (61%)	20 (14%)	104 (74%)	21 (15%)	15 (11%)	2 (1%)

* These numbers include 4 cæsarean sections from group 1.

clear that whereas the antibiotics have made surgical induction of labour potentially safe, the perinatal mortality cannot be kept to a minimum unless amniotomy is regarded as a serious surgical operation to be performed by an experienced operator in the operating-theatre; neither can it be achieved without the use of the physiological oxytocin drip, unless many more cæsarean sections are to be performed.

The Physiological or the Pharmacological Oxytocin Drip?

It has been postulated that the delivery of 5 milliunits of oxytocin a minute (1 unit added to the bottle, and 40 drops a minute) is the extreme range of the physiological drip, and for two reasons. The physiological concentration of oxytocin in the blood which institutes labour and effects delivery is comparable with that produced by the intravenous infusion of from 0·2 to 0·5 milliunit (and less than 1 milliunit) of commercial oxytocin a minute (Theobald 1958). The extreme range of the physiological drip is thus five times the maximum postulated physiological concentration of oxytocin in the blood. Secondly, we have proved over a period of 10 years, in well over 1000 patients, that the physiological drip is safe for any woman who is fit to go into labour. Its safety has recently been confirmed by Ryan (1958) although he used a slightly stronger concentration than I consider safe or necessary.

Lennon (1957), in a series of 987 surgical inductions, combined when necessary with the oxytocin drip, achieved a corrected perinatal mortality of 1·6% and a cæsarean-section rate of 2%. My only criticism of these admirable results is that he used a pharmacological oxytocin drip. The patient receiving such a drip cannot be left unwatched and even then I regard it as potentially dangerous, for the sensitivity of the human myometrium to oxytocin can increase a thousandfold in the space of a few hours.

It must be remembered that less than 20% of the midwifery of this country is done in teaching hospitals, and that in most non-teaching hospitals there is neither a doctor nor a medical student nor even a pupil midwife to sit by the patient. The pharmacological drip can, therefore, be employed only in a few hospitals, whereas the physiological drip can be used in every little hospital throughout the Commonwealth and also in private houses.

Lennon (1957) stated that 78% of his patients were delivered within 48 hours of induction, whereas 91% of our patients who did not require a drip were delivered within 24 hours (table v), and 66% of all patients who were given a drip were delivered within 24 hours of starting it. We used the pharmacological drip, and then never more than 2 units in the bottle, in only 20 out of 666 women in whom labour was induced, and half of them failed to be delivered per vaginam.

Since it is postulated that a woman does not go into labour until the myometrium becomes sensitive to physiological amounts of oxytocin, there must clearly be a point at which large amounts of this hormone will cause uterine activity when physiological amounts have no effect. Moreover it is probably relatively safer to give a pharmacological drip to a patient in whom the physiological drip would suffice than to a woman whose uterus is insensitive to oxytocin or shows incoordinate activity. My whole argument is that in practice the physiological drip is equally efficacious, it is safe, and it demands neither machine nor attendant to control it.

Is the Cure Worse than the Disease?

The crux of the whole problem is whether the cure is as bad as, or worse than, the disease. Nesbitt (1957), representing perhaps the majority view of obstetricians in the United States, affirms that less than a quarter of the fœtal deaths after term take place in utero before the onset of labour, and he concludes that " The hazards to the fœtus prior to the onset of labour are insufficient to outweigh the dangers of routine and often drastic measures to keep pregnancies from becoming postmature ". Similar views have recently been expressed in this country by Browne (1957), Macafee and Bancroft-Livingston (1957), Gibberd (1958), Wrigley (1958), and Cope and Pearson (1958). Their views are warranted by their results, for a perinatal mortality varying between 4% and 6% cannot be contemplated. I suggest that the disease is worse than they admit and that the cure is more satisfactory than they allow.

Conclusions

The number of healthy mature babies that can be saved by inducing labour is, I suggest, of the order of 1·2% of all hospital deliveries, of which 0·6% are saved from death from postmaturity. Many " unnecessary " inductions will of course be done, an occasional cord will prolapse, and a few women will fail to go into labour in a reasonable time. We are well content to perform this operation a hundred times in order to save 4 or even 2 healthy babies, as indeed we must to prevent death from postmaturity. The contemplative attitude advocated by Nesbitt (1957), Gibberd (1958), and Wrigley (1958) is no longer tenable; neither is the idea of a routine injection of radioactive isotopes into the uterus attractive.

No infant can be born until the membranes have ruptured (or been ruptured) nor without the help of oxytocin, the hormone devised by nature for this very purpose. If sweeping and rupture of the membranes, a purgative, an enema, and, if necessary, a physiological oxytocin drip, can save babies, lower the cæsarean-section and forceps rates, and almost eliminate prolonged labour, then surgical induction of labour, together with weekly antenatal care, must become the two main pillars of policy of the modern obstetric hospital.

The surgical induction of labour as described above is not meddlesome midwifery but the imitation of Nature. It is associated with a perinatal mortality of the order of 0·5% and deserves a wider use. When the factor, or factors, concerned in sensitising the human myometrium to oxytocin are discovered, the routine induction of labour at the end of the 38th week of pregnancy will become inevitable, for intact membranes are assuredly the greatest single hindrance to normal delivery. (See also Bainbridge, Nixon, and Smyth 1958.)

Maternity reports both from above and from below the Border tell of the great increase in the use of this operation during the last few years, particularly in the treatment of postmaturity. The important thing is not to try to stop this inevitable surge, but to direct it into physiological channels. It is preferable, if possible, to postpone amniotomy until the cervix is reasonably ripe. The procedure must be regarded as a serious surgical operation to be performed by a competent operator in the best possible surroundings, and requires the development of a hospital technique and ritual. An almost perfect procedure must not be spoiled by its casual and careless performance.

Such credit as our results deserve belongs to our registrars, Dr. H. A. Kelsey (now in Canada), Dr. J. E. B. Muirhead, Dr. R. E. ff. Devitt, and Dr. D. L. Flax, and to our nursing staff, who have had much to endure.

Tables I, V, and VI are reproduced from my chapter on Induction of Labour in the forthcoming edition of *British Obstetric Practice*

by kind permission of the editor, Sir Eardley Holland, and the publishers, Messrs. William Heinemann.

REFERENCES

Bainbridge, M. N., Nixon, W. C. W., Smyth, C. N. (1958) *J. Obstet. Gynæc. Brit. Emp.* **65**, 189.
Ballantyne, J. W., Browne, F. J. (1922) *ibid.* **29**, 192.
Bancroft-Livingston, G., Neill, D. W. (1957) *ibid.* **64**, 498.
Blaikley, J. B. (1956) *Amer. J. Obstet. Gynec.* **71**, 291.
Browne, F. J. (1957) *Brit. med. J.* i, 851.
Browne, J. C. McC., Veall, N. (1953) *J. Obstet. Gynæc. Brit. Emp.* **60**, 141.
Burnett, R. K. (1955) *Med. J. Aust.* **1**, 40.
Calkins, L. A. (1954) *Amer. J. Obstet. Gynec.* **68**, 50.
Clayton, S. G. (1941) *J. Obstet. Gynæc. Brit. Emp.* **48**, 460.
Clifford, S. H. (1954) *J. Pediat.* **44**, 1.
College of General Practitioners (1957) Obstetric Survey by South-west of England Faculty.
Cope, I., Pearson, M. G. (1958) *Brit. med. J.* i, 1211.
Daichman, I., Gold, E. M. (1954) *Amer. J. Obstet. Gynec.* **68**, 1128.
Drew Smythe, H. J. (1949) *J. Obstet. Gynæc. Brit. Emp.* **56**, 431.
Evans, G. (1954) *Lancet*, ii, 564.
Gibberd, G. F. (1958) *ibid.* i, 64.
Gibson, G. B. (1952) *J. Obstet. Gynæc. Brit. Emp.* **59**, 814.
— (1955) *Brit. med. J.* **2**, 715.
Greenhill, J. P. (1954–55) Year Book of Obstetrics and Gynecology. Chicago.
Hamilton, C. J. K. (1949) *J. Obstet. Gynæc. Brit. Emp.* **56**, 413.
Hill, G. (1952) *ibid.* **59**, 807.
Johnson, T., Clayton, C. G. (1955) *ibid.* **62**, 513.
Lennon, G. G. (1957) *Proc. R. Soc. Med.* **50**, 793.
Lindell, A. (1956) *Acta. obstet. gynec. scand.* **35**, 76.
Macafee, C. H. G., Bancroft-Livingston, G. (1958) *J. Obstet. Gynæc. Brit. Emp.* **65**, 7.
MacLennan, H. R. (1954) *Brit. med. J.* ii, 837.
MacKay, R. B. (1957) *J. Obstet. Gynæc. Brit. Emp.* **64**, 185.
Morris, N., Osborn, S. B., Wright, H. P. (1955) *Lancet*, i, 323.
— — — (1956) *ibid.* ii, 481.
Nesbitt, R. E. L. (1957) Perinatal Loss in Modern Obstetrics. Philadelphia.
Parker, R. B. (1957) *J. Obste.. Gynæc. Brit. Emp.* **64**, 94.
Racker, D., Burgess, G. H., Manly, G. (1953) *Lancet*, ii, 953.
Ryan, T. J. (1958) *J. Obstet. Gynæc. Brit. Emp.* **65**, 71.
Strand, A. (1956) *Acta obstet. gynec. scand.* **35**, 76.
Tennent, R. A., Black, M. D. (1954) *Brit. med. J.* ii, 833.
Theobald, G. W. (1958) *J. Physiol.* **141**, 30 P.
— Kelsey, H. A., Muirhead, J. M. B. (1956) *J. Obstet. Gynæc. Brit. Emp.* **63**, 641.
Turnbull, E. P. N., Baird, D. (1957) *Brit. med. J.* ii, 1021.
— Walker, J. (1955) *Arch. Dis. Childh.* **30**, 102.
Walker, J., Turnbull, E. P. N. (1953) *Lancet*, ii, 312.
Walker, J. (1954) *J. Obstet. Gynæc. Brit. Emp.* **61**, 162.
Wrigley, A. J. (1958) *Lancet*, i, 1167.

LUPOID HEPATITIS AND THE HEPATIC LESIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS

IAN R. MACKAY *
M.D. Melb., M.R.C.P., M.R.A.C.P.
ASSISTANT TO THE CLINICAL RESEARCH UNIT

L. I. TAFT *
M.B., B.Sc. Melb.
PATHOLOGIST TO THE CLINICAL RESEARCH UNIT

D. C. COWLING
M.D. Melb., M.R.A.C.P.
CLINICAL PATHOLOGIST

ROYAL MELBOURNE HOSPITAL

From the Clinical Research Unit of the Royal Melbourne Hospital and the Walter and Eliza Hall Institute of Medical Research, Melbourne, Victoria, Australia

A POSITIVE lupus erythematosus (L.E.) cell test may be obtained in cases of chronic hepatitis and cirrhosis (Joske and King 1955, Mackay et al. 1956, Wilkinson and Sacker 1957). We called this syndrome " lupoid hepatitis" and suggested that the L.E. phenomenon, rather than being a " non-specific " or " false positive " reaction, might represent evidence for abnormal antibody formation in chronic hepatitis; in turn, this may be responsible for the downward progress of the disease, and also for certain other lupus manifestations which may supervene in lupoid hepatitis (Taft et al. 1958).

We have attempted to assess the relationship of lupoid hepatitis to systemic lupus erythematosus (S.L.E.) by (*a*) reviewing the clinical and pathological features of 14 cases of lupoid hepatitis seen at the Royal Melbourne Hospital, and (*b*) analysing the incidence and type of liver involvement in 19 cases of classical S.L.E., particularly by study of histological material obtained at necropsy or by biopsy.

* Working with the aid of a grant from the National Health and Medical Research Council of Australia.

Case Material

Clinical and laboratory features of 14 cases of lupoid hepatitis are presented in table I. Cases L.H. 1-7 of lupoid hepatitis were described by Mackay et al. (1956), cases L.H. 9 and L.H. 13 by Gray et al. (1958), and cases L.H. 11-13 by O'Brien et al. (1958).

In 19 of 35 confirmed cases of S.L.E. observed in this hospital, liver tissue was available for histological study; these cases are described in table II.

Methods

Biochemical and laboratory methods, biopsy techniques, and the L.E. cell test employed have been previously described (Mackay et al. 1956). The autoimmune complement-fixation (A.I.C.F.) reaction was that described by Gajdusek (1958).

Features of Lupoid Hepatitis

Ætiological Factors

Like S.L.E., lupoid hepatitis occurs most frequently in young females, the 14 present cases including 9 females and 2 males below 40 years of age. In 5 cases the initial illness was compatible with acute infectious hepatitis, although case L.H. 7 was a munitions worker and handled toxic chemicals. 2 patients had chronic nutritional hepatitis due to alcoholism. In the remaining 7 cases jaundice developed insidiously after malaise and ill health, and no ætiological factors were recognised.

Clinical and Biochemical Features

These were as previously described (Mackay et al. 1956). The hepatitis was unusually severe and progressive, with recurrent exacerbations of jaundice and sometimes episodes of hepatic failure. The liver and particularly the spleen were enlarged, ascites was common, and spider nævi were prominent. Amenorrhœa was common in the females, but other major endocrine disturbances were not observed.

The biochemical tests of " liver function " were profoundly disturbed and the erythrocyte-sedimentation rate was increased. The serum-γ-globulin level was usually above 2 g. per 100 ml.—a finding in itself suggestive of an immunological disorder. Of 9 patients tested, 8 had elevated levels of plasma oxalacetic glutamic transaminase indicating liver-cell necrosis; in 4, highly elevated levels fell rapidly following administration of cortisone. This reduction of the liver damage by cortisone has been likened to the similarly rapid response to steroid therapy in immunologically determined conditions such as acquired hæmolytic anæmia (O'Brien et al. 1958).

Systemic Manifestations

7 of the 14 patients had joint pains of the polyarthritic type, and in 2 there was objective evidence of joint disease. Rashes were noted in 4 cases; in 1 the rash persisted over the typical butterfly area of the face and responded to chloroquin (fig. 1). A renal lesion developed in 3 cases; in case L.H.1, this closely resembled lupus nephritis (Taft et al. 1958), but in case L.H.4 it may have been related to coexisting mild diabetes mellitus. Case L.H.8 had an interstitial nephritis without glomerular lesions. Ulcerative colitis occurred in 3 cases: the relationship of this to chronic hepatitis has been discussed by Gray et al. (1958) of this unit. 2 patients had a pleural effusion, unassociated with pulmonary infection. Case

L.H.9 had hæmolytic anæmia with a positive Coombs test; there was clinical evidence of hæmolysis in case L.H. 3 and cold agglutinins were demonstrated, but the Coombs test was persistently negative. Lymphadenopathy, myocarditis, and thrombocytopenia each occurred in 1 case.

L.E.-cell Test in Lupoid Hepatitis

This test was usually weakly positive in that L.E. cells were found on single or infrequent occasions and usually only during active phases of the disease. Positive tests were not obtained with methods using anticoagulants. These findings were in contrast with classical cases of S.L.E. where the positive L.E.-cell test was readily obtainable and usually persisted throughout the illness. In 8 of the 14 cases, only one positive L.E.-cell test was obtained during the illness, although negative tests often showed tart cells and rosettes; in 5 of these 8 cases, only scanty L.E. cells were seen in the positive preparation. In the remaining 6 patients, however, the test was positive more than once, and it was repeatedly so in case L.H. 7.

Fig. 1—Woman, aged 29 (case L.H. 3) with nutritional hepatitis and positive L.E.-cell test, showing the rash of lupus erythematosus.

A.I.C.F. Reaction

10 cases were tested; the reaction was positive in 9, but weakly so in 5. Cases with high titres did not differ clinically from those with a weakly positive reaction. A similar high incidence (75%) of positive A.I.C.F. reactions was found in S.L.E.; positive reactions were obtained in 5 of 25 cases of active chronic hepatitis (L.E.-cell test negative) and in 2 of 18 cases of nutritional hepatitis (Mackay and Larkin 1958).

Cortisone Therapy

11 patients, including 3 reported by O'Brien et al. (1958), were treated with cortisone (table I). 4 received immediate and sustained benefit, and remain free of symptoms, and a 5th is in moderate remission. In 4 cases some improvement occurred, but this was either slight or unsustained and cortisone was discontinued after periods varying from two months to two years. In 2 cases no effect was apparent. As in other lupus manifestations, the value of cortisone may be in controlling acute exacerbations of the disease; it is uncertain whether long-term maintenance therapy either prevents or retards ultimate hepatic scarring.

Prognosis

We do not agree with Hill (1957) that lupoid hepatitis may represent a "benign" lupus manifestation. 8 of our 14 patients have died; liver failure occurred in 6 with an average course of three years, so the ultimate prognosis should be guarded.

Anatomical Changes in Lupoid Hepatitis

Liver biopsy was performed in 12 patients; in 10 this was done at the time of the positive L.E.-cell test. Necropsy was performed in 8 fatal cases including 1 case

TABLE I—FEATURES OF LUPOID HEPATITIS

Case (L.H.) no.[1]	Age (yr.)	Sex	Duration of illness (yr.)	Duration of observation (yr.)	Probable ætiology	Systemic manifestations	Serum-bilirubin[2] (mg. per 100 ml.)	Serum-albumin[2] (g. per 100 ml.)	Serum-globulin[2] (g. per 100 ml.)	Serum-γ-globulin[2] (g. per 100 ml.)	p.G.O.T. units[3]	E.S.R. (mm. in 1st hr.)[2] Westergren	Test for L.E. cells: No. positive	Test for L.E. cells: Strength[4]	Test for L.E. cells: No. negative	A.I.C.F. titre,[5] liver antigen	Steroid therapy: Maintenance dose (mg. per day)[6]	Steroid therapy: Duration (mos.)	Steroid therapy: Improvement[7]	Present health status
1	20	F	4	4	Viral	Colitis, glomerulonephritis	5·0	3·6	5·5	3·4	30	80	1	+	7	4	50	16	+	Death (liver failure)
2	21	F	3	2½	Viral	Facial rash	4·8	2·3	4·4	3·7	65	102	2	+	6	4	Not given			Death (liver failure)
3	29	F	6	5½	Nutritional	Rash, arthritis of knees, hæmolytic anæmia, thrombocytopenia	1·0	3·4	3·5	1·9	70	75	1	+	10	32	50	6	+s	Death (liver failure)
4	66	F	4	1	?	Diabetes mellitus, nephropathy	0·6	2·3	3·4	2·1	N.T.	106	1	+	4	64	p 10	7	±s	Death (cancer of stomach)
5	16	M	3½	2	?	None	2·0	3·2	4·2	3·0	125	N.T.	1	+	5	0	p 15	3	++	Moderately good
6	75	F	½	¼	Viral	None	8·8	1·9	5·4	2·6	N.T.	N.T.	1	++++	0	N.T.	Not given			Death (liver failure)
7	39	F	3½	3½	? Viral, ? toxic	Arthralgia, rash, stomatitis	2·8	3·4	5·1	4·3	70	76	11	++++	16	2048	100	44	++	Moderately good (L.E. cell test negative since Jan.,1957)
8	15	F	2	¼	?	Pleural effusion, pyelonephritis	2·0	2·3	5·1	N.T.	N.T.	9	1	++++	2	N.T.	50	2	±	Death (pneumonia, liver failure)
9	39	M	6	4	?	Arthralgia, scleroderma, ulcerative colitis, myocarditis, pleural effusion, lymphadenopathy	8·0	3·2	4·2	2·6	N.T.	120	2	++	1	N.T.	75	22	+	Death (congestive cardiac failure)
10	28	M	2½	¼	Nutritional	Rash, pneumonia	0·6	3·7	3·6	1·9	N.T.	N.T.	1	++	1	N.T.	Not given			Untraced
11	57	F	1	1	?	None	2·9	3·6	5·4	3·5	246	N.T.	3	++	0	4	p 30	10	+++	Good
12	15	M	4½	4½	?	Arthralgia, thrombocytopenic purpura	1·5	3·3	5·4	4·3	376	84	1	++	23	16	p 20	12	++	Fair
13	29	F	2	1¼	?	Polyarthritis, ulcerative colitis	2·3	1·6	4·5	2·6	544	90	3	+	7	4	75	7	+++	Good
14	13	F	2	¼	Viral	Arthralgia	4·8	2·9	3·6	1·9	900	54	2	++	6	8	100	1	±	Death (pneumonia, liver failure)

1. Cases L.H 1–4 and LH 7 were tabulated by Mackay and Gajdusek (1958) in different order.
2. Initial values.
3. Maximum values.
4. Numerous (++++), moderate (+++), or scanty (+) L.E. cells seen in L.E.-cell preparation.
5. Expressed as reciprocal.
6. p = prednisolone.
7. Considerable (++++), moderate (+++), slight (+), no change (±), side effects (s).

N.T. = not tested.

(L.H. 3) with nutritional hepatitis. In all, the liver was macroscopically and microscopically characteristic of active chronic hepatitis (Saint et al. 1953), and presented obvious regenerative nodules and diffuse fibrosis resembling the appearances of so-called "post-necrotic cirrhosis" (fig. 2). Additional histological features included active necrosis in 6 cases and active parenchymal-cell regeneration in 8 cases. In 9 cases there was a striking degree of cellular infiltration, mainly in the connective tissue; these cells, which sometimes formed dense aggregates and infiltrated the parenchymal nodules, consisted predominantly of lymphocytes, plasma cells, and histiocytes. In 3 cases cellular infiltration was less pronounced. Fatty infiltration was prominent in one biopsy (L.H. 3).

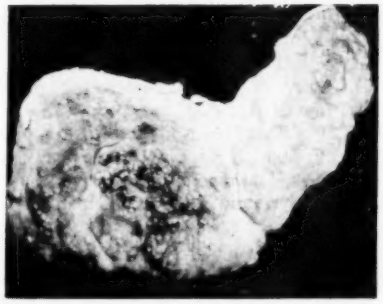


Fig. 2—Liver at necropsy from a girl, aged 13 (case L.H. 14), who presented with lupoid hepatitis 18 months after her sister contracted acute infectious hepatitis. There is considerable scarring and nodular regeneration.

Ulcerative colitis was present in 3 patients, and the morphological changes in the colon were characteristic. Ulcerative colitis and glomerulonephritis occurring in 1 case have been previously described (Taft et al. 1958). Knee-joint tissues were examined in 1 fatal case with severe arthralgia, but the changes were minor and non-specific.

Systemic Lupus Erythematosus with Liver Lesions

The incidence of histological lesions in the liver was assessed in 19 of 35 patients with classical S.L.E. admitted to the Royal Melbourne Hospital since 1953. The liver was enlarged in 39% of these cases—an incidence similar to that in other case series of S.L.E. (Mackay 1958). Since liver enlargement may be due to fatty change and congestion, and since serum-protein components may be disturbed by the disease itself, neither hepatomegaly nor abnormal "liver-function" tests provide satisfactory evidence of liver involvement in lupus, and liver tissue must be examined. Tissue was obtained by aspiration biopsy in 11 cases and at necropsy in 8 cases; clinical and biochemical details and histological findings are presented in table II.

TABLE II—FEATURES OF CASES OF SYSTEMIC LUPUS ERYTHEMATOSUS IN WHICH LIVER HISTOLOGY WAS STUDIED

Case no.[1]	Age (yr.)	Sex	Hepatomegaly	Evidence of liver disease	Serum-albumin[2] (g. per 100 ml.)	Serum-globulin[2] (g. per 100 ml.)	Serum-γ-globulin (g. per 100 ml.)	Cephalin flocculation[2]	Bromsulphalein retention (% of injected dose)	P.G.O.T. units	A.I.C.F. liver antigen (maximum titre)	Histological changes in liver[4]
L. 1	42	F	–	Nil[3]	4·1	2·7	1·4	+ + +	12	25	256	(b) Slight portal fibrosis, lymphocytic granuloma (see Mackay and Gajdusek 1958)
L. 2	56	F	+	Nil	3·3	2·1	N.T.	–	N.T.	N.T.	64	(b) Normal
L. 3	26	F	–	Nil	3·2	4·0	1·9	+ + +	24	57	64	(b) Portal infiltration,[4] liver-cell necrosis, fat
L. 4	25	F	–	Nil	4·0	3·5	1·8	+ + +	2	10	64	(b) Normal
L. 5	25	F	+	Telangiectasia	3·1	4·2	2·8	+ + +	10	42	16	(b) Considerable portal fibrosis and infiltration
L. 7	41	F	+	Hepatic venous congestion; telangiectasia[3]	3·4	3·1	2·0	+ + +	37	18	8	(b) Slight portal infiltration and fibrosis; bile-duct proliferation
L. 8	22	F	–	Classical "viral" hepatitis 8 weeks prior to onset of disease	3·7	2·7	1·6	+	N.T.	11	8	(b) Minimal fat deposition
L. 9	39	F	–	Nil (renal failure)	1·9	2·1	0·8	+ + +	N.T.	N.T.	8	(n) Portal infiltration, fat deposition, congestion
L. 13	29	F	–	Nil (renal failure)	0·5	3·0	0·2	N.T.	N.T.	N.T.	0	(n) Congestion
L. 14	31	F	–	Nil (renal failure)	3·3	2·4	N.T.	N.T.	N.T.	N.T.	0	(n) Congestion, central necrosis
L. 16	50	M	+	Thrombocytopenic purpura, splenectomy; severe ulcerative colitis, colectomy; active chronic hepatitis with recurrent jaundice (Gray et al. 1958, case 6)	3·3	5·3	2·5	+ + +	N.T.[5]	51	64	(b) Liver-cell necrosis and nodular regeneration; considerable cellular infiltration and diffuse fibrosis
L. 17	28	F	+	Acute acquired hæmolytic anæmia, splenectomy; "silent" nodular cirrhosis detected at laparotomy	3·9	3·5	1·8	–	N.T.	57	512	(b) Nodular liver; considerable fibrosis, mild cellular infiltration
L. 20	35	F	+	Nil	3·9	3·5	1·6	+ + +	8	12	0 (8 with kidney antigen)	(b) Slight portal infiltration and fibrosis
L. 23	20	F	–	Nil (renal failure)	3·2	3·0	0·7	+ + +	N.T.	9	8	(n) Slight portal infiltration and fibrosis; congestion
L. 33	42	M	–	Nil (renal failure)	2·8	3·5	0·9	+ +	13	7	0	(n) Moderate portal infiltration; congestion
La	28	F	+	Nil[3]	4·2	3·3	1·6	+ + +	N.T.	N.T.	N.T.	(n) Portal infiltration and congestion
Lb	50	M	+	Nil	2·4	4·6	2·1	+ +	N.T.	N.T.	N.T.	(b) Slight portal infiltration and fibrosis; halo nuclei
Lc	49	F	–	Nil	3·9	2·6	1·4	+	N.T.	N.T.	N.T.	(n) Congestion
Ld	38	F	+	Nil	3·5	3·3	N.T.	N.T	N.T.	N.T.	N.T.	(n) Considerable portal infiltration

1. Case designations and sequential order of cases follow that in previous papers (Mackay and Gajdusek 1958, Mackay and Larkin 1958), excepting cases La, Lb, Lc, Ld.
2. Initial values.
3. Jaundice due to hæmolytic episodes.
4. The cell types were predominantly lymphocytes, plasma cells, and histiocytes.
5. Icteric.
6. (b) biopsy; (n) necropsy.

N.T. = not tested.

Pathological Changes in the Liver

In 6 of the 19 cases the liver was either normal or the changes were entirely non-specific; congestion was present in 5 necropsy cases. Minor changes in 11 cases included portal-tract fibrosis with mild to moderate cellular infiltration; in addition there was lobular distortion and bile-duct proliferation in 2, lymphocytic granuloma in 1, focal necrosis in 1, and slight fat accumulation in 5 of these biopsies. Thus, minor changes in the liver were found in over half the cases, but these per se would not give rise to clinical or biochemical manifestations.

In 2 patients a nodular cirrhosis of the liver was incidentally discovered at laparotomy. In 1 (L. 17) biopsy showed coarse fibrosis but no necrosis and little regeneration or cellular infiltration. The biopsy from case L. 16 showed active hepatitis with pronounced fibrosis and distortion of lobular structure, regeneration, and cellular infiltration. Subsequently this patient displayed the clinical and biochemical features of active chronic hepatitis (Gray et al. 1958, case 6).

Discussion

We distinguished lupoid hepatitis from classical systemic lupus erythematosus because the liver disease is the initial and dominant lesion and determines the poor prognosis with death in liver failure; other systemic manifestations, if present, are usually limited; typical rashes are uncommon; and anatomically the appearances in lupoid hepatitis are those of multinodular cirrhosis. However, varying degrees of systemic involvement did occur in lupoid hepatitis, and 2 cases subsequently displayed such diffuse lesions that the ultimate diagnosis was debatable.

On the other hand, liver involvement in true S.L.E., which we term " hepatic lupus ", has been stated to be uncommon and non-significant (Harvey et al. 1955, Kofman et al. 1955). Histological abnormalities were present in 13 of our 19 cases of classical S.L.E., but were mainly mild and comprised portal infiltration and fibrosis and a single granuloma; Kofman et al. (1955) reported similar findings in a series of 11 cases. However, 2 cases, which had been previously diagnosed clinically as S.L.E., showed the macroscopic and microscopic changes of active chronic hepatitis; thus, morphologically the livers were those of lupoid hepatitis. Although the clinicopathological pictures of lupoid hepatitis and S.L.E. with liver involvement may differ, the occurrence of intermediate cases with overlapping features in both groups suggests that the pathogenesis of the two conditions may be similar.

Close study of cases of lupoid hepatitis may provide clues as to why active chronic hepatitis pursues its relentless course. The original illness may be clinically and epidemiologically recognisable as a severe, mild, or even anicteric acute viral hepatitis which fails to recover; the process may also be initiated by other liver damaging processes such as alcoholic malnutrition. In other cases the onset is insidious, no initiating illness can be recognised, and there is no clinical event correlating with the morphologically derived term " postnecrotic cirrhosis ". The relapsing course of progressive hepatitis, often attributed to continuing viral activity or to ischæmic necrosis secondary to vascular derangements (Baggenstoss 1957), may depend upon an immunological anomaly; this is suggested by the findings of hypergammaglobulinæmia (Zimmerman et al. 1951), marrow plasmacytosis (Jarrold and Vilter 1949), the occasional occurrence of a positive L.E.-cell test (indicating antinuclear antibody formation), a positive A.I.C.F. test, dense lymphocyte and plasma-cell infiltrations in the liver, and finally the sensitivity of the liver-necrosing process to cortisone (O'Brien et al. 1958).

The A.I.C.F. reaction detects the presence of serum-globulins which react immunologically with human organ antigens. The reaction is positive in about 75% of cases of both systemic lupus erythematosus and lupoid hepatitis, but neither the effective antigen nor antibody have been identified. Since A.I.C.F. titres do not correlate quantitatively with the clinical course it seems unlikely that these antibodies are responsible for episodes of tissue damage, and they may even occur adventitiously as a response to extensive tissue necrosis. At present we regard positive A.I.C.F. reactions as evidence for an underlying disorder in the antibody-producing system.

Dense plasma-cell and lymphocytic foci were prominent in the portal tracts in cases of lupoid hepatitis, and to a lesser extent in hepatic lupus. This appearance has been aptly described by More and Movat (1958), in connection with polyarteritis nodosa, as " the morphological counterpart of antibody production ". With regard to the immunological and histological findings, a tempting analogy can be drawn between lupoid hepatitis and Hashimoto's thyroiditis, in which the plasma-cell and lymphocyte accumulations may represent local sites of antibody formation (Doniach and Roitt 1957). Thus these cellular infiltrations might have a close bearing on the pathogenesis of lupoid hepatitis, lupus erythematosus, and allied disorders. An analogous process may be broadly invoked to explain certain other conditions characterised by plasma-cell and lymphocytic accumulations, such as Miculicz disease, Sjögren's disease, non-tuberculous Addison's disease, and primary biliary cirrhosis. We prefer to call diseases which may be due to autoantibody production " autoclastic " (self-destroying) rather than " collagen " diseases, particularly since body components other than collagen may be implicated (Mackay 1958).

Although data are accumulating favouring the immunological pathogenesis of lupoid hepatitis, direct evidence for this is still scanty, particularly at the laboratory level, and moreover it is doubtful whether this pathogenesis may justifiably be extrapolated to cases of active chronic hepatitis or postnecrotic cirrhosis. Should this immunological concept of lupoid hepatitis be valid, we still do not know whether liver injury, viral or nutritional, initiates an autoimmune reaction subsequently directed against normal liver cells, or whether abnormal antibody production depends more upon a primary disorder of the antibody-producing system.

Summary

14 cases of lupoid hepatitis (active chronic hepatitis with a positive L.E.-cell test) are described. The clinical, biochemical, and pathological features were predominantly those of severe progressive hepatitis. Minor systemic manifestations occurred in 8 cases.

Histological examination of the liver in 19 cases of systemic lupus erythematosus showed normal tissue or non-significant changes in 6 and minor changes (portal fibrosis and cellularity) in 11 cases; only 2 cases had typical chronic hepatitis.

Lupoid hepatitis and lupus erythematosus may be distinguished as separate entities by the clinical findings and pathological changes; but the occurrence of overlapping features in the two groups suggests a similar patho-

genesis, possibly mediated via abnormal immunological responsiveness with auto-destruction of host tissues. Lupoid hepatitis may represent a specific example of a fundamental disease process which we term autoclasia—" self-breaking-down ".

We wish to thank Dr. Sara Weiden and Miss Lois Larkin for laboratory assistance, and physicians of the honorary medical staff of the Royal Melbourne Hospital for kindly allowing us to study patients under their care. Sister I. Langford rendered valuable assistance.

REFERENCES

Baggenstoss, A. H. (1957) *J. Amer. med. Ass.* **165**, 1099.
Doniach, D., Roitt, I. M. (1957) *J. clin. Endocrin.* **17**, 1293.
Gajdusek, D. C. (1958) *Arch. intern. Med.* **101**, 9.
Gray, N. J., Mackay, I. R., Taft, L. I., Weiden, S., Wood, I. J. (1958) *Amer. J. digest Dis.* **3**, 481.
Harvey, A. M., Shulman, L. E., Tumulty, P. A., Conley, C. L., Shoenrich, E. H. (1955) Systemic Lupus Erythematosus. Baltimore.
Hill, L. C. (1957) *Brit. med. J.* ii, 655.
Jarrold, T., Vilter, R. W. (1949) *J. clin. Invest.* **28**, 286.
Joske, R. A., King, W. E. (1955) *Lancet*, ii, 497.
Kofman, S., Johnson, G. C., Zimmerman, H. J. (1955) *Arch. intern. Med.* **95**, 669.
Mackay, I. R. (1958) *Med. J. Aust.* ii, 279.
— Gajdusek, D. C. (1958) *Arch. intern. Med.* **101**, 30.
— Larkin, L. (1958) *Aust. Ann. Med.* **7**, 251.
— Taft, L. I., Cowling, D. C. (1956) *Lancet*, ii, 1323.
More, R. H., Movat, H. Z. (1958) *J. Path. Bact.* **75**, 127.
O'Brien, E. N., Goble, A. J., Mackay, I. R. (1958) *Lancet*, i, 1245.
Saint, E. G., King, W. E., Joske, R. A., Finckh, E. S. (1953) *Aust. Ann. Med.* **2**, 113.
Taft, L. I., Mackay, I. R., Larkin, L. (1958) *J. Path. Bact.* **75**, 399.
Wilkinson, M., Sacker, L. S. (1957) *Brit. med. J.* ii, 661.
Zimmerman, H. J., Heller, P., Hill, R. P. (1951) *New Engl. J. Med.* **244**, 245.

THE SYNDROME OF BRACHYMETACARPAL DWARFISM (" PSEUDO-PSEUDOHYPOPARATHYROIDISM ") WITH AND WITHOUT GONADAL DYSGENESIS

J. J. VAN DER WERFF TEN BOSCH
M.D. Leiden

RESEARCH ASSISTANT IN THE DEPARTMENT OF ENDOCRINOLOGY, UNIVERSITY HOSPITAL, LEIDEN

HYPOCALCÆMIA in cases of pseudohypoparathyroidism is thought to be due to lack of sensitivity to endogenous parathyroid hormone on the part of the " target " tissues of this hormone (Albright et al. 1942). Diagnostic proof of pseudohypoparathyroidism depends on the demonstration of parathyroid-resistant hypocalcæmia.

Apart from the clinical and chemical abnormalities which pseudohypoparathyroidism has in common with idiopathic hypoparathyroidism, the former condition is characterised by some, but not necessarily all, of the following features: short stature, short metacarpal and metatarsal bones, roundness of the face, and subcutaneous calcifications. These abnormalities are apparently unrelated to the hypocalcæmic state, and may arise independently in individuals without tetany and with normal serum calcium and phosphorus values.

The term pseudo-pseudohypoparathyroidism was first used in 1952 by Albright, Forbes, and Henneman, when they described a 29-year-old single woman, of short stature, who had had irregular menstrual bleedings at 2–6 months' intervals from the menarche at the age of 12. In addition this woman had a " round " face, subcutaneous calcinosis, and brachydactylia caused by underdeveloped metacarpal bones; she had no tetany or hypocalcæmia.

Further examples of pseudo-pseudohypoparathyroidism were soon recognised by others, and at least five more cases have now been reported. The second of these (Miles and Elrick 1955) was a married, nulliparous woman of 24, who had had only one or two scanty menstrual periods each year since the menarche at the age of 15. There were subcutaneous calcifications in the man described by McNeely et al. (1956), but not in the cases of Miles and Elrick (1955) and Roche (1955), nor in the two sisters reported by Seringe and Tomkiewicz (1957). Calcinosis is also an inconstant finding in pseudohypoparathyroidism (Elrick et al. 1950). The round face is an ill-defined feature and was clearly displayed only by the patients of Albright et al. (1952) and of Miles and Elrick (1955).

Fig. 1—Pseudo-pseudohypoparathyroidism with gonadal dysgenesis (case 3).

The description of a syndrome which consists of multiple defects will inevitably be followed by the observation of *formes frustes*, and the designation pseudo-pseudohypoparathyroidism betrays the ambiguous descent of this syndrome. It is clearly essential to define a syndrome by its characteristic features. But soft-tissue calcifications were present in only one case reported after the original description and this patient lacked the round face. What, then, constitutes the basic entity in pseudo-pseudohypoparathyroidism?

The only abnormalities common to the six cases quoted above were a reduced stature and brachydactylia due to a developmental anomaly of the metacarpal and metatarsal bones. There is uniformity in the incidence of the lesion in different metacarpals. Elrick et al. (1950), in an analysis of pseudohypoparathyroidism, commented upon the distribution of the metacarpal defect as opposed to that in myositis ossificans progressiva. Whilst metacarpal shortening in pseudohypoparathyroidism was found predominantly in the 4th and 5th metacarpal bones, in myositis ossificans progressiva the lesion was almost restricted to the thumb. There is also a predilection for the lateral metacarpals in the patients described as examples

TABLE I—SUMMARY OF THE FINDINGS IN THE EIGHT CASES REPORTED

Case no.	Sex		Age (yr.)	Height (cm.)	Urinary gonadotrophins (mouse units)	Serum		Comments
	Phenotype	Oral mucosa				Phosphate (mg. per 100 ml.)	Calcium (mg. per 100 ml.)	
1	F	M	8½	108	<6	4·1	9·6	
2	F	M	15	127	>90	4·2	10·3	Primary amenorrhœa, no calcinosis
3	F	M	18	140	>90	4·2	10·8	Primary amenorrhœa
4	F	Unknown	14	125	6–90	3·8	10·9	Primary amenorrhœa
5	F	F	14	143	6–90	3·8	10·9	Menarche at 13 years, no calcinosis
6	F	Unknown	17	142		4·0	10·9	Menarche at 13 years
7	M	Unknown	49	158		3·3	10·2	Subcutaneous calcinosis
8	M	Unknown	18	153		3·8	10·0	No calcinosis

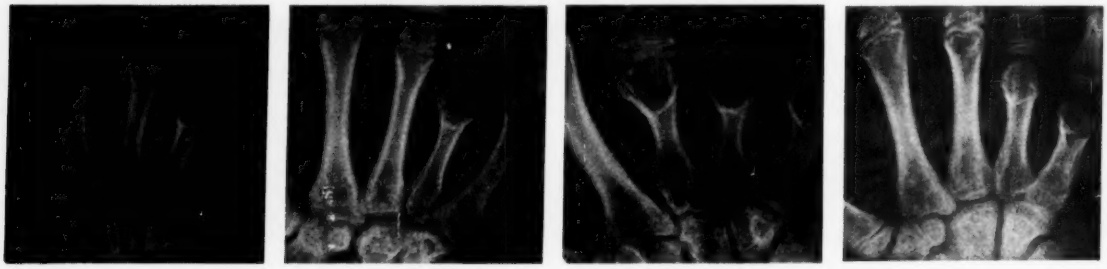


Fig. 2—Radiographs of the metacarpals of cases 1–4.

of pseudo-pseudohypoparathyroidism. Thus in both hands of the six cases quoted the 1st metacarpal was involved five times, the 2nd metacarpal twice, the 3rd metacarpal seven times, the 4th metacarpal ten times, and the 5th metacarpal seven times.

Observations

The following is a brief report on eight patients. Some of the relevant data are summarised in table I.

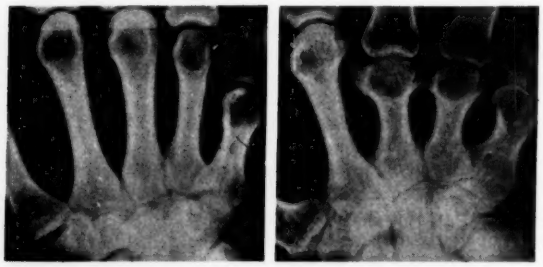


Fig. 3—Radiographs of the metacarpals of cases 6 and 7.

All the patients were dwarfed. None showed clinical evidence of tetany, and the serum levels of calcium and phosphorus were normal. The face was undoubtedly rounded in some of the patients, especially cases 6 and 7, who were grossly obese.

The diagnosis of gonadal dysgenesis seems unquestionable in three girls (cases 1–3) who were of male nuclear sex as determined by smears of oral mucosa (table I). Case 4 had many external signs of the syndrome of gonadal dysgenesis. Radiographs of part of the hands of these four patients (fig. 2), show clearly that in each case one or more of the lateral metacarpal bones is underdeveloped. A study of the hands of twenty-five other cases of gonadal dysgenesis failed to show abnormal metacarpal bones. Thus the abnormality existed in four out of twenty-nine cases of gonadal dysgenesis.

The other four patients were sexually mature. Cases 5 and 6 had menstrual periods, and the two male patients (cases 7 and 8) had normal external genitalia and a masculine distribution of body hair. There was no evidence for or against fertility in any of them. Case 7 had severe skeletal decalcification and subcutaneous calcinosis, with ectopic bone formation. Fig. 3 shows the radiographs of cases 6 and 7 with typical short metacarpal bones. In cases 5 and 8 (fig. 4) the proximal epiphyses of the middle phalanges were also deformed.

It is of interest that case 5 is a younger sister of case 8. Radiographs have been made of the hands of their mother, a sister aged 20, the twin sister of case 8, and two younger brothers aged 12 and 11; all showed normal metacarpal bones. Cases 5 and 8 looked very much alike and very different from their relatives. Both had an oval face, with a diffuse and almost cyanotic flush, and thin scalp hair. Case 5 had never needed a haircut. Their blood-pressures were normal and their scleræ were not blue.

Discussion

Pseudo-pseudohypoparathyroidism has been put forward as a distinct clinical entity, with the physical characteristics of pseudohypoparathyroidism but without the chemical disturbance which causes tetany. Dwarfism, metacarpal defects, and subcutaneous calcinosis characterise both these conditions. But, since calcinosis and metacarpal defects may be absent in pseudohypoparathyroidism (Elrick et al. 1950), its derivative pseudo-pseudohypoparathyroidism clearly calls for a more critical definition.

Strictly speaking the diagnosis of pseudo-pseudohypoparathyroidism applies only to one (namely, the first) case, since all the cases reported later lacked at least

Fig. 4—Radiographs of the hands of cases 5 and 8 to show abnormalities of the metacarpals and of the middle phalanges.

TABLE II—COMPARISON BETWEEN SOME OVERLAPPING SYNDROMES

—	Short stature	Short metacarpals	Subcutaneous calcinosis	Tetany
Hypoparathyroidism	—	—	—	+
Pseudohypoparathyroidism	+	±	±	+
Pseudo-pseudohypoparathyroidism	±	+	±	—
Gonadal dysgenesis	±	+	? ±	—
Myositis ossificans progressiva	—	(+)	+	—

+ = present. — = absent. (±) = present, but differently located.

one of the original characteristics. Our case 7 comes closest to the original description, having both calcinosis and a notably rounded face (and incidentally, also a high blood-pressure) but he differs in sex.

In view of the findings in the six cases quoted from the literature and in our eight cases, it seems sensible to reserve the term pseudo-pseudohypoparathyroidism for the condition associated with reduced stature and shortness of the lateral metacarpal bones, without symptoms or signs of tetany. It is very unfortunate, as Fromm (1956) has already pointed out, that the name pseudo-pseudohypoparathyroidism has been introduced into medical writing to denote a set of congenital abnormalities which bear no relation to the parathyroid glands. A more descriptive name, which would be applicable to all these cases might be *brachymetacarpal dwarfism* (without tetany). Subcutaneous calcinosis may or may not be present, and gonadal dysgenesis is another possible abnormality within the syndrome. Table II summarises the conditions which share some of these congenital abnormalities.

It may be significant that the first two reports of pseudo-pseudohypoparathyroidism concerned women with menstrual disorders (see above), and it would be interesting to know the nature of their gonadal dysfunction. Hoffenberg et al. (1957) have described cases of gonadal dysgenesis with regular menstrual cycles, and we have seen a patient of male nuclear sex who has had irregular bleedings for some time.

One further point of interest concerns the cause of the disturbance of growth. The early childhood growth pattern in gonadal dysgenesis fulfils the criteria of "primordial" dwarfism—i.e., retarded height development associated with normal skeletal maturation—which is the type of growth that might be expected if there is deficiency of growth hormone only. On the other hand Albright et al. (1942) produced evidence suggesting an insensitivity of the target tissues to parathyroid hormone in cases of pseudohypoparathyroidism. It will be interesting to see whether, if human growth hormone becomes available in the near future, it will stimulate height development in cases of gonadal dysgenesis and in pseudohypoparathyroidism and pseudo-pseudohypoparathyroidism.

Summary

Pseudo-pseudohypoparathyroidism has never been adequately defined. It is suggested that the term be reserved for patients of short stature, with shortness of the lateral metacarpal bones, but without tetany. Subcutaneous calcinosis may or may not be present.

This report concerns eight further examples of the syndrome, four of whom also had gonadal dysgenesis. This indicates that gonadal dysgenesis, like subcutaneous calcinosis, may be associated with pseudo-pseudohypoparathyroidism.

The term *brachymetacarpal dwarfism* (without tetany) is offered as an alternative, strictly descriptive, designation.

I am indebted to Prof. A. Schaberg, of the Department of Experimental Histology and Cytology, for the examination of oral mucosal smears, and to Prof. A. Querido for his kind interest and criticism.

REFERENCES

Albright, F., Burnett, C. H., Smith, P. H., Parson, W. (1942) *Endocrinology*, **30**, 922.
— Forbes, A. P., Henneman, P. H. (1952) *Trans. Ass. Amer. Phycns*, **65**, 337.
Elrick, H., Albright, F., Bartter, F. C., Forbes, A. P., Reeves, J. D. (1950) *Acta endocr., Copenhagen*, **5**, 199.
Fromm, G. A. (1956) *J. clin. Endocrin.* **16**, 293.
Hoffenberg, R., Jackson, W. P. U., Muller, W. H. (1957) *ibid.* **17**, 902.
McNeely, W. F., Raisz, L. G., LeMay, M. (1956) *Amer. J. Med.* **21**, 649.
Miles, J., Elrick, H. (1955) *J. clin. Endocrin.* **15**, 576.
Roche, M. (1955) *ibid.* p. 964.
Seringe, P., Tomkiewicz, S. (1957) *Sem. Hôp. Paris*, **33**, 1092 P.

INTRA-ARTICULAR PREDNISOLONE 21 : PHOSPHATE

A CLINICAL TRIAL

B. G. B. CHRISTIE
M.B. Lond., D.Phys.Med.
SENIOR REGISTRAR, DEPARTMENT OF PHYSICAL MEDICINE, ST. THOMAS' HOSPITAL, LONDON, S.E.1

ONE of the greatest advances in the management of diseases of joints has been the introduction of corticosteroids in a form suitable for intra-articular injection. Until recently, however, the substances used have been in the form of suspensions, with the exception of hydrocortisone hemisuccinate. Since prednisolone 21 : phosphate, which is freely soluble in water, has been available for intra-articular injection, this pilot trial was undertaken to estimate its value in patients with joint disease. The solution used contained prednisolone 21 : phosphate in a concentration of 25 mg. per ml.

The Trial

The aim was to test the effect of prednisolone 21 : phosphate when injected into a joint which is painful and swollen. 48 intra-articular injections were made in thirty-six patients with the following diseases:

Group	Diagnosis	No. of joints
I	Rheumatoid arthritis (active phase)	16
II	Osteoarthritis (primary degenerative joint disease)	22
III	Osteoarthritis (secondary to rheumatoid disease)	4
IV	Systemic lupus erythematosus	6

In most cases the knees were selected because of the simplicity of intra-articular injection in this joint. All the patients had an exacerbation of symptoms in the joint at the time of injection. The joints injected and the doses of prednisolone 21 : phosphate were:

Joint	Knee	Elbow	Wrist	Hip	Shoulder	1st metatarso-phalangeal	Ankle
Dose (mg.)	50	25	25	75	75	25	25
No.	37	3	3	2	1	1	1

On one or more previous occasions 32 of the 48 joints had been injected with hydrocortisone acetate, and the response was known. In some patients where both knees were involved, one was injected with prednisolone 21 : phosphate and the other with hydrocortisone acetate. In comparative trials of this nature strict control is almost impossible to achieve, as conditions vary from patient to patient, and from time to time in the same patient.

Results

These results were assessed as good, moderate, poor, or as a failure, according to the following criteria:

Good—complete relief of pain, and decrease in joint swelling and tenderness lasting for more than a week.

Moderate—complete relief of symptoms (as above) for less than a week, or partial relief for more than a week.

Poor—slight relief of symptoms lasting less than a week.

Failure—no response.

Group	Good	Moderate	Poor	Failure
I	5	2	4	5
II	7	5	4	6
III	2	2	..	..
IV	..	..	2	4
Total	14	9	10	15

Of the 15 joints injected without effect, 6 had previously responded well to hydrocortisone. Three patients in whom hydrocortisone had previously been ineffective responded well to prednisolone 21: phosphate.

Rapidity of action.—Prednisolone 21: phosphate acted quicker than hydrocortisone acetate. Kendall (1958) gave the average time before the onset of relief as 30 hours when using hydrocortisone acetate, and $20^1/_2$ hours with prednisolone acetate. In this series the comparable figure for prednisolone 21: phosphate was 18 hours.

Duration of action.—In those patients in this series who had previously had successful injections of hydrocortisone acetate, the average period of relief was 20 days, but in those who responded to prednisolone 21: phosphate the average relief was $10^1/_2$ days.

Side-effects.—One patient developed a generalised urticaria 3 days after an injection, but this rapidly subsided when an antihistaminic drug was given. Although there was no previous history of allergy, this reaction may have been unassociated with the prednisolone 21: phosphate because of the long interval between the injection and the onset of symptoms.

Pain after injection.—Pain arose in twelve joints (25%) after injection, and was severe in two, moderate in one, and slight in nine. It lasted less than 12 hours in three, 12–48 hours in five, and 48 or more hours in four.

Conclusions and Summary

When injected into joints, prednisolone 21: phosphate was not as effective as hydrocortisone acetate. The response was of shorter duration than that of hydrocortisone, but often more dramatic. There was pain after intra-articular injection in 25% of patients as compared with about 50% of patients having hydrocortisone acetate. The rapidity of the intra-articular action of prednisolone 21: phosphate appears to exceed that of any previous steroid.

In evaluating these results it must be borne in mind that prednisone and prednisolone are four to five times as potent as their precursors, and in this trial they were used in an equivalent weight-for-weight dosage. The present cost of prednisolone 21: phosphate exceeds that of hydrocortisone acetate.

Prednisolone 21: phosphate, therefore, does not supplant hydrocortisone acetate in the treatment of joint lesions, but it may be valuable in patients who are refractory to hydrocortisone.

The value of prednisolone 21: phosphate in the treatment of soft-tissue lesions is being investigated elsewhere. The lower incidence of pain after injection may be an indication for its use in these conditions.

I should like to thank Dr. Philippe Bauwens, physician-in-charge of the department of physical medicine, St. Thomas' Hospital, for permission to publish this work, and Glaxo Laboratories Ltd. for supplying the prednisolone 21: phosphate.

REFERENCE

Kendall, P. H. (1958) *Brit. med. J.* ii, 290.

URINARY OSMOLALITY AND SPECIFIC GRAVITY

L. C. ISAACSON

M.B., B.Sc. Cape Town, M.R.C.P.E.

RESEARCH FELLOW, CHEMICAL SECTION OF THE DEPARTMENT OF MEDICINE, THE UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE, PHILADELPHIA

As a measure of the concentrating-power of the kidney, urinary osmolality is more exact than specific gravity. The correlation between them is close enough to ensure the continued use of specific gravity in everyday clinical medicine, if not in the laboratory. But some striking disparities have come to light (Miles et al. 1954, Corcoran 1955, Joekes et al. 1957); and I have therefore examined these two parameters of renal function.

Urine is largely a solution of common inorganic salts, urea, and a small amount of other organic matter. This latter fraction accounts for only 20–30% of its total specific gravity (Price et al. 1940.) As the inorganic salts ionise readily, the osmolality of a urine sample is determined largely by the concentrations of the inorganic salts The relationship between osmolality and specific gravit was determined for each of a number of dilutions of the common urinary inorganic salts, urea, and glucose. The results are shown graphically. Within the limits shown the osmolality/specific-gravity ratio remains constant for all salts, regardless of their concentration.

Price et al (1940) have also shown that when simple salt solutions are added to each other or to urine the specific gravity of the new solutions can be foretold by simple addition and dilution.

There are no complex physicochemical forces at work. Dilution of weak electrolyte solutions increases their ionisation and hence their osmolality. Changes in pH also affect

TABLE I—MIXTURE OF SIMPLE SALTS AND UREA

Salt	Volume (ml.)	Osmolality (milliosmoles per litre)
NH_4Cl	146	322
$NaHCO_3$	50	620
K_2HPO_4	190	145
KH_2PO_4	100	317
Urea	178	810

Expected total osmolality—424 milliosmoles per litre.
Observed total osmolality—418 milliosmoles per litre.

TABLE II—ADDITION OF SALT MIXTURE TO RANDOM URINES

Urine		Urine with equal volume of mixture of salts*	
		New osmolality	
Specimen no.	Osmolality	Expected	Obtained
1	754	512	505
2	317	294	289
3	372	322	321
4	644	458	455
5	373	322	321
6	438	355	354

* The salt mixture was a freshly prepared dialysing solution, as prepared for use with the artificial kidney. The mixture contained Na, K, Ca, Mg, and HCO_3 in physiological proportions, as well as glucose and lactate: its osmolality was 271 milliosmoles per litre.

TABLE III—ADDITION OF ONE RANDOM URINE TO THREE OTHER SAMPLES

Urine		Urine with equal volume of "stock" urine*	
		New osmolality	
Specimen no.	Osmolality	Expected	Observed
1	274	315	315
2	798	577	571
3	395	385	386

* The osmolality of the stock urine was 356 milliosmoles per litre.

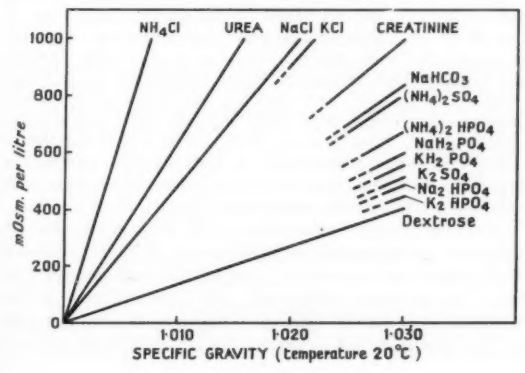
osmolality, but over the range of pH and solute concentrations of urine, these factors are negligible. Osmolality therefore might be expected to change parallel with specific gravity; but since undetermined organic constituents are present in urine, it was necessary to confirm this assumption. Price's experiments were repeated in simplified form, measuring osmolality rather than specific gravity (tables I–III). The deviations from values arrived at by addition and dilution fall within the limits of experimental error.

The osmolality of a urine sample can thus be regarded largely as the sum of the osmolalities of the individual solutions of the various inorganic salts and urea.

Recently Joekes et al. (1957) succeeded in inducing physiological oliguria with a "fixed" specific gravity. In their experiment the urines had specific gravities fixed between 1·008 and 1·014 and osmolalities of 400–600 milliosmoles per litre. For this range of specific gravity the osmolarity was thus "considerably higher than the generally supposed isosmolarity with plasma". The reason for this lack of correlation between specific gravity and osmolarity becomes clear from the graph.

A mixture of simple salts with a specific gravity of 1·008–1·014 could not attain an osmolality of 400–600 milliosmoles per litre unless it consisted predominantly of urea, NaCl, or KCl. The acid salts, with the exception of NH_4Cl, have a much lower osmolality/specific-gravity ratio and would inevitably lower the total osmolality. NH_4Cl, on the other hand, has a distinctively high ratio: indeed, a solution with a specific gravity of 1·008 approaches the maximum osmolality that human urine can reach. That the excretion of large amounts of NH_4Cl caused the discrepancy noted by Joekes et al. is further suggested by consideration of the conditions under which the experiments were performed: normal subjects were put on a low-salt, low-nitrogen, low-calorie diet. The excretion of NH_4 would soon build up to a maximum.

The graph also throws light on some long-recognised clinical phenomena. The invalidity of urinary specific gravity as a measure of renal concentrating-power in the presence of glycosuria is well known. Ziegler and Brice (1937) in a study of 10,000 cases also noted that the "average" alkaline urine had a lower specific gravity than the "average" acid urine. This might be explained by the greater osmolality/specific-gravity ratio of $NaHCO_3$ than of the acid salts. (NH_4Cl is an exception, but it is not normally formed in large amounts.) Finally, the sameness of the specific gravity of plasma ultrafiltrate and urine in chronic renal insufficiency can be recognised as fortuitous. As individual osmolality/specific-gravity ratios differ greatly only at high concentrations, the proportion of one salt to another can differ considerably without much affecting the final specific gravity in mixtures with a total osmolality of 300–400 milliosmoles per litre, or less. This is particularly so when NH_4 and urea are present in low concentration, as in the urine of patients with renal insufficiency. The "fixed" specific gravity of such a urine, and its closeness to the specific gravity of plasma ultrafiltrate, is therefore no indication of chemical similarity or proof of its "glomerular-filtrate-like" composition.



Summary

The osmolality of a specimen of urine can be regarded as the sum of the osmolalities of its constituent solutions.

Osmolality/specific-gravity relationships were determined for the common urinary inorganic salts, urea, and glucose.

These ratios allow a clearer understanding of some apparent discrepancies between urinary osmolality and specific gravity.

My thanks are due to Dr. G. D. Webster, Jr., Dr. J. R. Elkinton, and Dr. L. W. Bluemle of the chemical section of the department of medicine, Hospital of the University of Pennsylvania, for helpful criticism and advice.

REFERENCES

Corcoran, A. C. (1955) *J. Lab. clin. Med.* **46**, 141.
Joekes, A. M., Mowbray, J. F., Dormandy, K. (1957) *Lancet*, ii, 864.
Miles, B. E., Paton, A., de Wardener, H. E. (1954) *Brit. med. J.* ii, 901.
Price, J. W., Miller, M., Hayman, J. M. (1940) *J. clin. Invest.* **19**, 537.
Ziegler, E. E., Brice, A. T. (1937) *Ann. intern. Med.* **11**, 768.

DANGERS OF URIC-ACID EXCRETION DURING TREATMENT OF LEUKÆMIA AND LYMPHOSARCOMA

D. GREENBAUM
M.B. Lond., M.R.C.P.
MEDICAL REGISTRAR

H. F. HOPE STONE
M.B. Lond., D.M.R.T.
SENIOR REGISTRAR, DEPARTMENT OF RADIOTHERAPY

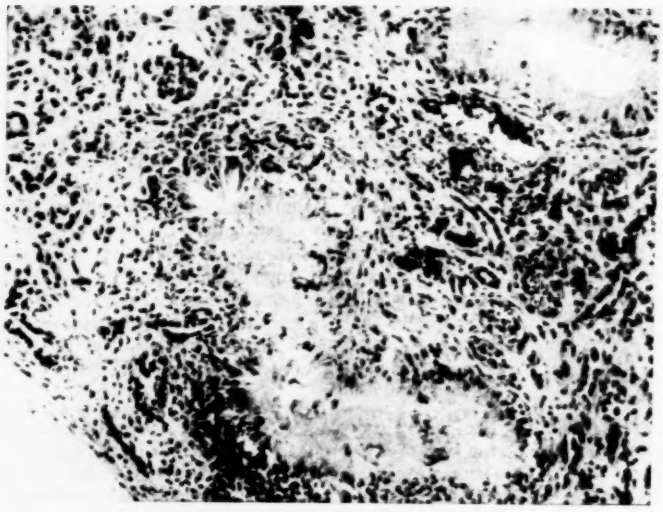
LONDON HOSPITAL, E.1

THE production of uric acid is often increased in leukæmia and related conditions. When radiotherapy and cytotoxic drugs accelerate this process the precipitation of uric acid in the renal tract can be a serious or even fatal complication.

Case-reports

Case 1.—A boy of 14 was admitted to the London Hospital on May 5, 1956. Laparotomy a month earlier had revealed a large tumour in his cæcum and ascending colon, histologically a lymphosarcoma. Throughout his stay in hospital—even before radiotherapy was given—he had repeated attacks of pain, redness, and swelling in various joints. This was strongly suggestive of gout.

Radiotherapy was begun on June 8. A three-field mid-abdominal bath was used (open fields 60 cm. focal skin distance, 250 kV., half value layer 1·7 mm. copper) increasing the daily input by 25r from 25 to 100r. Although fairly well at the beginning of treatment, within a few days the boy was seriously ill. He vomited, became drowsy, developed spontaneous bruises, and had nose-bleeds. His urinary output fell



Deposits of uric-acid crystals in renal tubules in case 1.

to less than 400 ml. daily; and this could not be accounted for either by the vomiting or by a small fluid intake. Radiotherapy was stopped on June 15, after a total of 660r (tumour-dose) had been given. Two days later the blood-uric-acid was 16·7 and the blood-urea 330 mg. per 100 ml. A specimen of urine showed no abnormality, except for large quantities of uric-acid crystals. The patient's clinical condition gradually improved: vomiting stopped, and urine output returned to normal. On June 26 his blood-uric-acid was 8·5 and his blood-urea 85 mg. per 100 ml.

A week later radiotherapy was recommenced; but, within three days, vomiting began again, the daily urine output fell to 100 ml., the blood-uric-acid rose to 30 and the blood-urea to 258 mg. per 100 ml. Serum-potassium was 9·1 mEq. per litre. The patient died on the fourth day, after a total of 300r tumour-dose had been given. The abdominal tumour had changed only slightly under treatment.

At necropsy several lymphosarcomatous deposits were found in the abdominal cavity. The kidney surfaces were heavily mottled with pinpoint white dots: these extended as streaks into the medulla. Histological examination showed extensive deposits of uric-acid crystals in the tubules with surrounding cellular reaction and necrosis (see figure). There was no evidence of other kidney disease or of urinary obstruction by growth. Chalky white deposits were found in and around many joints.

Case 2.—A man of 49 has been attending the London Hospital since 1952 when he was found to have chronic lymphatic leukæmia. An unusual feature of his illness, and his principal disability, was enormous enlargement of the spleen. The peripheral white-cell count has always been less than 20,000 cells per c.mm., predominantly lymphocytes. When the discomfort of the splenomegaly became intolerable, radiotherapy was given: he received seven courses in all between 1952 and 1957. On the first three occasions, three direct fields to the spleen were used (250 kV., 50 cm. focal skin distance, half value layer 1·7 mm. copper) with an incident dose varying from 125r in each field in twenty-two days, to 200r in seven days. On the last four occasions an upper-abdominal-bath technique was used, the tumour dose varying from 35r in a single treatment to 600r in eighteen days. These courses had no clinical ill effects, but often they had to be curtailed because of severe leucopenia and thrombocytopenia. The spleen usually shrank considerably, if only temporarily, under treatment. In June, 1957, two months after one of the courses, the patient complained of attacks of pain, redness, and swelling in various joints. His blood-uric-acid was 6·8 mg. per 100 ml.

He was admitted to the London Hospital on Feb. 20, 1958, for his eighth course of radiotherapy. The spleen at this time was enlarged almost down to the pelvic brim: his hæmoglobin was 62%, his white-cell count 14,000 (92% lymphocytes), and his platelet-count 34,000 per c.mm. A three-field abdominal bath was used (open fields 80 cm. focal skin distance 220 kV). The daily incident dose was increased by 5r from 5 to 30r. After the spleen had been irradiated with 155r tumour-dose, the patient began to complain of intermittent aching pain in the left loin. By this time the spleen had diminished to two fingerbreadths below the umbilicus and the peripheral white-cell count had fallen to 5400. Next day the pain in the loins became so severe as to make him roll about in bed. He passed little urine, and specimens contained blood and heavy deposits of uric-acid crystals. The blood-uric-acid and blood-urea were 16·7 and 108 mg. per 100 ml. respectively. The symptoms could be attributed to urinary obstruction by uric-acid crystals, and fluids and sodium lactate were given by mouth and intravenously. Recovery was rapid: three days later the blood-uric-acid was 8·8, and seven days later 5·3 mg. per 100 ml. The patient later remarked that his urine had always contained a lot of " gravel " while he was having radiotherapy.

A further course of radiotherapy was given in March, using 20 × 20 cm. anterior and posterior fields, with an incident dose of 110r in each field, in three treatments. On this occasion the patient drank large quantities of fluid and his urine was made alkaline with sodium citrate. There were no ill effects, but radiotherapy was stopped after the white-cell count had fallen to 850 per c.mm. The two courses of treatment reduced the spleen to one handbreadth below the costal margin. Subsequent urine examination, renal-function tests, and intravenous pyelography showed no abnormality.

Discussion

A patient with chronic leukæmia and one with lymphosarcoma developed oliguria and uric-acid crystalluria, associated with a high blood-uric-acid, shortly after starting radiotherapy. The complication was reversed by discontinuing treatment, but subsequent courses had the same ill effects. There seems little doubt that renal damage or urinary obstruction by uric-acid crystals was the immediate cause of the first patient's death. The second patient only suffered severe renal colic, but his transient oliguria and raised blood-urea were warning signs. Both patients had symptoms suggestive of gout before treatment.

More than forty years ago Goodall (1914) observed that uric-acid excretion in a patient with myeloid leukæmia increased during treatment with a cytotoxic substance (Cooley toxin); and Lennox and Mears (1923) noted a similar rise in a patient receiving radiotherapy for acute leukæmia. This was quantitatively confirmed by Sandberg et al. (1956). Bedrna and Polcack (1929) reported urinary obstruction by uric-acid stones in 2 patients; and cases of fatal blockage or kidney damage were described by Merrill (1940), Lear and Oppenheimer (1950), Kravitz et al. (1951), Weisberger and Persky (1953), and Fisher et al. (1958). In most of these, evidence of uric-acid obstruction appeared within a few days of beginning radiotherapy or cytotoxic drug-treatment.

The high blood-uric-acid levels are partly due to failure of excretion but probably more to the breakdown of liberated nucleoproteins. Leukæmia cells are particularly rich in these substances, and they are very radiosensitive: this may be why the complication does not arise in the treatment of other forms of malignant disease.

The uric-acid crystals may be deposited in any part of the renal tract: our photomicrograph shows them in the tubules.

Clinically the complication may start with renal colic, hæmaturia, oliguria, vomiting, drowsiness, or the passage of cloudy urine. (The urine of both our patients contained heavy deposits of uric-acid crystals.) It appears to be very uncommon, but minor examples go undiagnosed. Why it occurs in a few cases is not known: the intensity of treatment, the mass and radiosensitivity of the leukæmic tissue, the acidity of the urine, the fluid intake, and previous renal disease may be important factors. Patients, moreover, who have had gouty symptoms before, or who have a raised blood-uric-acid, seem to be especially prone to it.

Treatment is not difficult provided the condition is recognised in time. Vomiting during radiotherapy should not be taken for granted and pain in the side does not always arise in the spleen. Discontinuation of radiotherapy or cytotoxic drug-treatment, and the giving of large quantities of fluid and alkalis may forestall urinary obstruction; but ureteric catheterisation has occasionally been required. Some authors have suggested that the fluid intake should be increased and the urine made alkaline as a prophylactic routine in all patients who are irradiated for leukæmia or related conditions.

Summary

The massive excretion of uric acid, which sometimes complicates the treatment of leukæmia and lymphosarcoma, may have serious effects. Two such cases are reported: in one the complication ended in death. Timely recognition is essential if renal failure is to be avoided.

We should like to thank Dr. R. R. Bomford, Dr. J. A. Orr, and Prof. D. S. Russell for permission to publish.

REFERENCES

Bedrna, J., Polcack, J. (1929) *Med. Klinik.* **25**, 1700.
Fisher, S. M., Torre, A. V., Wohl, G. T. (1958) *Radiology*, **70**, 84.
Goodall, H. W. (1914) *Boston med. surg. J.* **170**, 789.
Kravitz, S. C., Diamond, H. D., Cramer, L. F. (1951) *J. Amer. med. Ass.* **146**, 1595.
Lear, H., Oppenheimer, G. D. (1950) *ibid.* **143**, 1595.
Lennox, W. G., Mears, J. H. (1923) *Arch. intern. Med.* **32**, 705.
Merrill, D. (1940) *New Engl. J. Med.* **222**, 94.
Sandberg, A. A., Cartright, G. E., Wintrobe, M. M. (1956) *Blood*, **11**, 154.
Weisberger, A. S., Persky, L. (1953) *Amer. J. med. Sci.* **225**, 669.

AORTIC THROMBOSIS CAUSING HYPERTENSION

H. S. SHUCKSMITH
T.D., M.B., B.Sc. Leeds, F.R.C.S.
SURGEON

G. WILSON
M.B. Leeds, F.R.C.S.
SENIOR REGISTRAR

GENERAL INFIRMARY AT LEEDS

HYPERTENSION is an infrequent complication of thrombosis at the aortic bifurcation (Leriche 1946) unless there is some occlusion of one or both renal arteries (Rob 1956, Wyatt and Felson 1957).

In the case reported here, hypertension developed slowly in a woman with aorto-iliac thrombosis, and the hypertension was controlled by thromboendarterectomy of the aorta between the renal arteries and by insertion of an aortic bifurcation homograft communicating with the two common femoral arteries.

Case-record

A woman, aged 52, was first seen in July, 1954, because of intermittent claudication for eight years affecting the thighs, calves, and ankles after walking 30 yards. Her weight was 122 lb., her blood-pressure 180/70 mm. Hg. The pulse was absent in both common femoral arteries, but the nutrition of the toes was normal. Translumbar aortography showed that the aorta was blocked 1½–2 in. below the renal arteries, and there was no filling of the arteries distal to the block (fig. 1). Six months later the patient was unable to walk more than 4 yards before the pain stopped her.

Fig. 1—Translumbar aortogram, showing the aortic block.

Operation—Resection of the aortic bifurcation was planned; but in March, 1955, when the aorta was exposed, it was found that the thrombus extended up to the level of the renal arteries. On the score of lack of previous experience of aortic resection in such circumstances, it was decided to perform bilateral lumbar sympathectomy as a palliative measure.

Course—Postoperative symptomatic improvement was enough to permit the patient to do some housework; but in September, 1956, she started to have severe headaches. The body-weight had increased to 161 lb., and the previously normal blood-pressure was raised to 210/110 mm. Hg. The urine (specific gravity 1·010) contained albumin. The blood-urea was 45 mg. per 100 ml., and the intravenous pyelogram showed no abnormality. A restricted diet led to reduction of weight to 147 lb. by January, 1958, when she could slowly walk 100 yards before the onset of claudication, although the headaches were increasing in severity. Recordings of the blood-pressure during the last three months of 1957 varied from 230/115 to 205/140 mm. Hg. Intravenous pyelography early in 1958 showed slightly less filling in the left kidney than in the right, but the sodium-excretion test (Connor et al. 1957) did not show any difference of pathological significance between the two kidneys (sodium 45 mg. per 100 ml. right kidney, sodium 40 mg. per 100 ml. left kidney). After being told the cause of her symptoms and the probable prognosis, the patient agreed to undergo another operation.

Second operation—In March, 1958, under general anæsthesia and hypothermia, the common femoral arteries were first exposed and their walls proved to be soft and free from atheromatous plaques. The aorta was then exposed through a midline incision, and the thrombosed portion was divided about 2 inches below the level of the renal arteries. Manual compression was applied to the proximal segment of the divided aorta through the lesser sac and thromboendarterectomy carried out by blunt dissection. Adherent and calcified plaques were removed with Desjardin's forceps and good bleeding was established. Before the release of manual compression

Fig. 2—The mass of calcified material removed from the proximal aorta.

a clamp was applied to the cleared portion of the aorta below the renal arteries. An aortic bifurcation homograft was then anastomosed to the proximal segment of the aorta. The limbs of the homograft were taken down retroperitoneally and then behind the inguinal ligaments, and each anastomosed end-to-side to the respective common femoral artery by Cockett's method. No pulsations were seen in the graft when the aortic clamp was released. Manual compression of the aorta in the lesser sac was reapplied, and through a longitudinal incision in the aortic portion of the graft about $^1/_2$ inch below the proximal anastomosis a Parker's intestinal clamp was passed upwards to withdraw a large mass of calcified material (fig. 2) from the proximal aorta. After closure of the incision in the graft good pulsation through the graft was established, and twelve hours later the popliteal and ankle pulses were palpable.

Progress—A small pulmonary infarction occurred on the tenth postoperative day, and the patient was discharged from hospital on the twenty-third postoperative day, her blood-pressure then being 140/90 mm. Hg. Two months later the patient reported that her walking was no longer impeded in any way and that she was free from headaches. The blood-pressure has remained at 140/90 mm. Hg., but the urine still contains a trace of albumin.

Discussion

Hypertension in association with aortic thrombosis is relatively uncommon. Starer and Sutton (1958) found that of 32 patients with aortic thrombosis only 2 had a diastolic pressure exceeding 120 mm. Hg. Of our series of 23 patients, only 2 had a diastolic pressure of more than 100 mm. of Hg. In coarctation of the aorta the hypertension is the result of the increased peripheral resistance caused by the stenosis and the collateral circulation, and it is not related to any renal pressor mechanism (Bing et al. 1948). The relative infrequency of hypertension in association with aorto-iliac thrombosis indicates that, when it does occur, it is not related to an increased peripheral resistance but is caused by renal ischæmia. One or both renal arteries may be narrowed by atherosclerosis, or the aortic atherosclerosis and thrombosis may involve the orifices of the renal arteries. An indication of reduction of the calibre of the renal arteries may be obtained by studying any disparity seen on the excretion pyelograms or from a difference in the volume and sodium content of the urine excreted by each kidney (Connor et al. 1957); and the reduction may be demonstrated by aortography (Poutasse and Denton 1957, De Camp and Birchall 1958). Aortography was not repeated in the present case because the sodium-excretion test had not shown any appreciable difference between the two kidneys. These findings were compatible with the idea that the renal ischæmia was caused by a central block in the aorta between the orifices of the renal arteries.

The condition of the common femoral arteries contrasted remarkably with the extensive aorto-iliac disease, because the walls of the femoral arteries were only a little softer than normal, and there were no atheromatous plaques. Probably the complete aorto-iliac block of several years' duration, and the consequent low blood-pressure and the absence of turbulence in the common femoral arteries, prevented the development of atheroma. It is noteworthy, too, that the patient's walking distance improved during the period of our observation, suggesting that the distal vessels in the leg were of reasonable calibre.

Removal of the grumous material from the aorta by curettage through an incision dividing the thrombosed aorta below the renal arteries is crude but effective (Freeman et al. 1954). But this relatively blind procedure is not without risk, and emboli produced by the operation may block a renal artery and so cause persistent hypertension for relief of which nephrectomy has been required (Wyatt and Felson 1957, Stone et al. 1957). Although the blind procedure does avoid extensive exposure of the aorta and interrupts the renal circulation only for a short time, it is desirable that thromboarterectomy at this level should be carried out under direct vision. Through an abdominothoracic incision the splenic flexure of the colon is retracted medially and the aorta can then be exposed proximal to the renal arteries. Incision in the aorta between the renal arteries permits inspection of the orifice of each renal artery while the aorta is clamped above or below the superior mesenteric artery.

Summary

Hypertension developed in a woman under observation on account of aorto-iliac thrombosis.

Hypertension and claudication were relieved by thromboendarterectomy and the insertion of an aorto-femoral bifurcation homograft.

Atheroma was absent in the common femoral arteries.

Blind thromboendarterectomy was successful, but in the region of the renal arteries thromboendarterectomy under direct vision is recommended.

REFERENCES

Bing, R. J., Handelsman, J. C., Campbell, J. A., Griswold, H. E., Blalock, A. (1948) *Ann. Surg.* **128,** 802.
Connor, T. B., Berthrong, M., Thomas, W. C., Jr., Howard, J. E. (1957) *Bull. Johns Hopk. Hosp.* **100,** 241.
De Camp, P. T., Birchall, R. (1958) *Surgery*, **43,** 132.
Freeman, N. E., Leeds, F. H., Elliot, W. G., Roland, S. J. (1954) *J. Amer. med. Ass.* **156,** 1077.
Leriche, R. (1946) Thromboses Artérielles. Paris.
Poutasse, E. F., Denton, H. P. (1957) *J. Amer. med. Ass.* **165,** 1521.
Rob, C. (1956) *Brit. med. J.* ii, 1027.
Starer, F., Sutton, D. (1958) *ibid.* i, 1255.
Stone, P. W., McNally, J. B., Lord, J. W., Hinton, J. W. (1957) *New Engl. J. Med.* **256,** 1076.
Wyatt, G. M., Felson, B. (1957) *Radiology*, **69,** 676.

CARCINOMA OF THE LINGUAL THYROID TREATED WITH RADIOACTIVE IODINE

W. A. MILL
M.S. Lond., F.R.C.S.
SURGEON IN CHARGE, E.N.T. DEPARTMENT, ROYAL MARSDEN HOSPITAL, LONDON, S.W.3

N. F. C. GOWING
M.D. Lond.
DIRECTOR, DEPARTMENT OF MORBID ANATOMY AT THE HOSPITAL

BRIAN REEVES
F.R.C.S.E.
CONSULTANT E.N.T. SURGEON, SALISBURY GROUP HOSPITALS

D. W. SMITHERS
M.D. Cantab., F.R.C.P., F.F.R.
DIRECTOR, RADIOTHERAPY DEPARTMENT, ROYAL MARSDEN HOSPITAL; PROFESSOR OF RADIOTHERAPY IN THE UNIVERSITY OF LONDON

A YOUNG married woman was first seen by one of us (B. R.) in June, 1956, when she was 24 years old. She had a lingual thyroid swelling, but no certain evidence of malignancy was found microscopically in a biopsy specimen removed by diathermy on June 14.

History

Up to the age of 19 she did not menstruate, but she then received some injections and her menstrual periods were regular until she became pregnant.

In February, 1955, when 7 months pregnant, she complained of a feeling of "a strawberry" sticking in her throat. She had one brisk hæmorrhage from the mouth at that time, but nothing abnormal was noticed and the feeling disappeared after delivery.

When she was 3 months pregnant for the second time, she had another brisk hæmorrhage.

In November, 1956, when 8 months pregnant, she had a third hæmorrhage. The swelling was a good deal larger and part of it was removed for biopsy. The report was: "Recurrent neoplasm of lingual thyroid, now certainly malignant; invasion and ulceration of epithelium, poorly

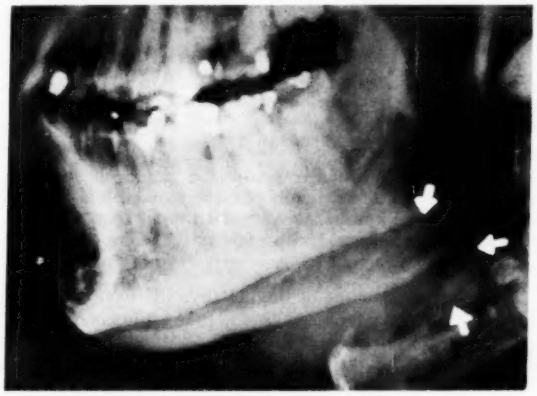


Fig. 1—Radiograph showing soft-tissue tumour at base of tongue

formed gland tubules, abnormal cells and mitotic figures. Plane of diathermy excision passes through the growth." On Dec. 14, 1956, the tumour was found to be still enlarging rapidly. Cæsarean section and sterilisation were performed.

She came to the Royal Marsden Hospital (case no. 030334) a fortnight later, on Dec. 28. Her voice was gruff and she had some difficulty in swallowing. At the base of the tongue was a mass 2·5 cm. in diameter, overhanging the epiglottis; its surface was ulcerated and bled

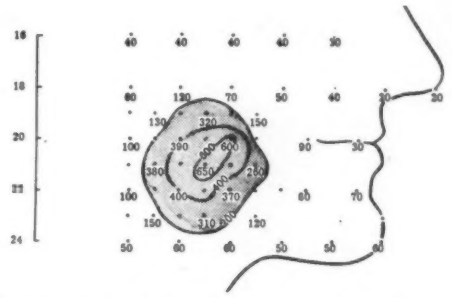


Fig. 2—Concentration of radio-iodine in lingual thyroid shown on a lateral scan 27 hours after tracer dose of ^{131}I (January, 1957).

easily (fig. 1). Two days later a radioactive iodine tracer dose of 500 μc. was given, and the patient was seen to have no normal thyroid, the iodine concentrating well in the tumour on the back of the tongue (figs. 2 and 3). Her basal metabolic rate was −15%, and her serum-cholesterol 464 mg. per 100 ml.

It was decided to treat her with radioactive iodine. Surgical removal would have been mutilating; external irradiation was much less likely to be effective; uptake of radioactive iodine in the tumour was good; and there was no genetic hazard.

Treatment and Progress

A therapeutic dose of radioactive iodine, 161 mC, given on Jan. 7, 1957, had a rapid effect on the tumour. By the fourth day the mass was reduced to nearly half its size and a distinct membrane had formed over it. Thereafter regression was slower; but by the middle of February only a small residual plaque could be felt on the back of the tongue and there was no uptake of radioactive iodine (fig. 4). She had signs of myxœdema, and was gaining weight.

On Feb. 20, 1957, she was given thyroid extract, gr. 2 daily, later increased to gr. 3. In October, 1957, she was well but still rather overweight. The dose of thyroid was increased to gr. 4 daily, on which she has been maintained satisfactorily since.

There is now no sign of any residual tumour.

Histopathology of Biopsy Specimen

Different areas of the biopsy specimen varied considerably in histological structure. The surface epithelium was exten-

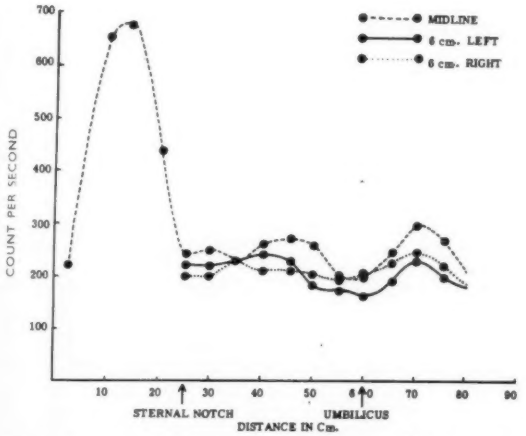


Fig. 3—Concentration of radio-iodine shown on a profile scan 26 hours after tracer dose of ^{131}I (January, 1957).

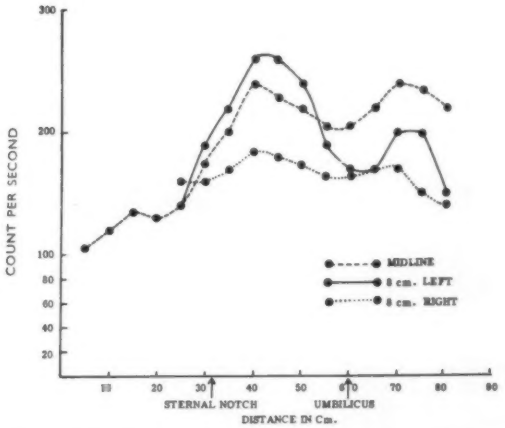


Fig. 4—Concentration of radioiodine shown on a profile scan 24 hours after tracer dose of ^{131}I (April, 1957).

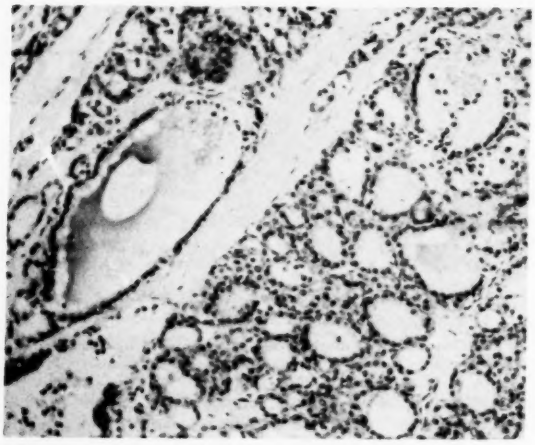


Fig. 5—Photomicrograph of biopsy specimen showing thyroid tissue composed of irregular acini containing palely stained colloid. (Hæmatoxylin and eosin. × 85.)

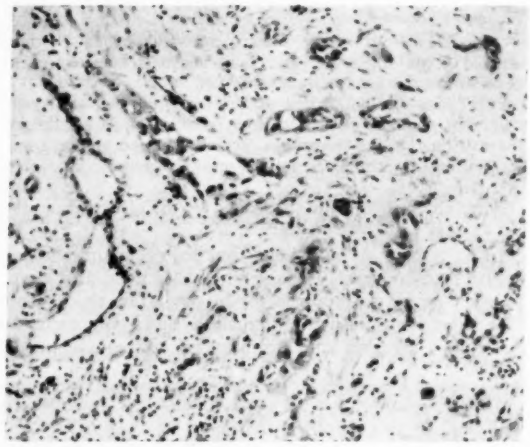


Fig. 6—Photomicrograph of another area of the biopsy specimen showing irregular groups of poorly differentiated tumour cells in an abundant stroma. There is a mild lymphocytic infiltrate. (Hæmatoxylin and eosin. × 85.)

sively ulcerated and replaced by a thick layer of fibrinous exudate which contained bacterial colonies in its superficial layer. Beneath the surface there was an ill-defined nodule of thyroid tissue. In some fields the follicles were closely packed and possessed small lumina containing a little palely staining colloid (fig. 5). The nuclei were large and vesicular; they were somewhat irregular in shape and many had prominent eosinophilic nucleoli. Occasional mitoses were present. The stroma was delicate and contained many thin-walled capillary blood-vessels. Other fields showed a few larger acini separated by broad bands of fibrous tissue. The least differentiated parts of the tumour consisted of small solid clumps of large epithelial cells which had eosinophilic cytoplasm and aberrant nuclei; these cell groups were growing in an abundant collagenous stroma infiltrated with a few inflammatory cells (fig. 6).

Discussion

The reported cases of lingual thyroids have been well reviewed by Montgomery (1935, 1936), Buckman (1936), and Goetsch (1948).

Montgomery, using rather strict criteria, accepted 144 cases

REPORTED CASES OF CARCINOMA OF THE LINGUAL THYROID

Author	Date of report	Sex and age of patient	Reported as	Previous history	Subsequent history
Ray	1918	M.74	Carcinomatous transformation of a lingual goitre.	3 years' enlargement.	Tumour removed, patient died. Necropsy.
Hofer	1920	M.47	Tongue goitre undergoing malignant degeneration.	Tumour recurred 3 years after first removal.	Recurrence removed. No subsequent history.
Tyler	1923	M.54	Carcinoma of lingual thyroid.	Primary 8 years; metastases in lungs.	X-ray and radium therapy; patient died. Necropsy.
Ashhurst and White	1925	M.56	Adenocarcinoma of lingual thyroid.	20 years; recurrent primary and nodes.	Recurrent tumour removed. Patient well several months. No follow-up.
Peracchia	1927	M.56	Struma maligno della base linguale.	18 months' dysphagia; metastasis in lymph-node.	Tumour removed with node. No subsequent history.
Marchal et al. ..	1935	M.59	Adéno-cancer d'un vestige thyroïdien de la langue.	Over 2 years; recurrent primary and multiple metastases.	Patient died. Necropsy.
Willis	1953	M.26	Carcinoma of lingual thyroid.	Several months' dysphagia.	Tumour removed, recurred; patient died. No necropsy.
Gunn	1910	F.18	"Undoubtedly carcinomatous"—Dr. W. G. Harvey and Prof. Scott.	—	Tumour removed. No subsequent history.
Rutgers	1910	F.21	Adenoma malignum.	—	Radical removal. Patient well for 3 years.
Brentano	1911	F.42	Probably lingual thyroid carcinoma with metastases in neck nodes.	9 years; recurrent primary and nodes.	—
Seelye	1916	F.18	Encephaloid carcinoma of aberrant or accessory thyroid.	—	Patient well 8 months after removal by wire snare.
Levi and Hankins	1935	F.21	Low-grade carcinoma invading tongue muscle.	A few days' rapid growth.	Complete extirpation. Patient well 9 months.
Watson and Pool ..	1940	F.86	Cancer of lingual thyroid origin.	—	Tumour removed. Patient well 5 years.
Wapshaw	1942	F.20	"Neoplastic and locally malignant"—Prof. J. Shaw Dunn. Clinically benign.	13 years, with recent enlargement.	Tumour removed. Patient well 18 months.
Mill et al.	1958	F.24	Poorly differentiated carcinoma of lingual thyroid.	2 months, and during previous pregnancy.	Radio-iodine therapy. Patient well after nearly 2 years.

M.=male. F.=female.

as authentic, while Buckman collected 241 from the literature and added one of his own. Goetsch presented three new female patients with lingual goitre, aged 30, 12, and 8 years, with histology resembling that of a "fetal adenoma" in two cases and a "colloid goiter" in the third. Two of these patients had clinical evidence of hypothyroidism.

Like other authors, Goetsch suggested that thyroid insufficiency is usually responsible for hypertrophy of any lingual thyroid tissue, since about two-thirds of the patients reported with this condition have no demonstrable thyroid gland in the neck. The demands of adolescence and pregnancy are other factors which may precipitate hypertrophy of a lingual thyroid.

The histological appearances of lingual thyroid goitre are very variable. The structure may be: (1) normal thyroid tissue; (2) similar to that of a "fœtal" adenoma; (3) like that of a "colloid" goitre; (4) that of an adenomatous or nodular goitre with the degenerative changes commonly seen in cervical goitre of this type.

Malignant change in a lingual thyroid is a great rarity. The *reported* cases of lingual thyroid cancer are listed in the table. Most of these cases are difficult to analyse because of inadequate clinical and histological details, lack of complete necropsy studies, or incomplete follow-up data. With the possible exception of Brentano's (1911) case, no metastasising lingual thyroid carcinoma was reported until 1923 (Tyler). Wapshaw (1942) and Goetsch (1948) both state that no authentic case of metastasising lingual thyroid cancer has been reported in a woman; we have also been unable to find such a record. The lingual nodule from Wapshaw's patient was described by Prof. J. Shaw Dunn as "neoplastic and locally malignant", but Wapshaw concluded that it was "clinically benign" since there had been no recurrence after two years.

The microscopical appearances of the biopsy material in our case certainly indicate a malignant neoplastic process, and from the histological standpoint we feel that a diagnosis of carcinoma is justified. Nevertheless it is clear from the literature that these lingual tumours in women may behave rather more benignly than many cervical thyroid carcinomas, and have a more favourable prognosis. More information is required, however, for any proper assessment of the natural history of such rare cases.

Summary

A case is reported of a lingual thyroid tumour, histologically malignant, in a young woman. This tumour appeared during two successive pregnancies and enlarged rapidly after the termination of the second.

A tracer dose of ^{131}I concentrated in the tumour, and treatment with radio-iodine was therefore carried out. This resulted in rapid regression of the lesion, which has shown no sign of recurrence after almost two years of observation.

The few previously reported cases of lingual thyroid carcinoma are reviewed and the relatively favourable prognosis of those so far seen in women is again emphasised.

It is a pleasure to record our thanks to Dr. H. E. Harding, director of pathology, Salisbury Area, who kindly supplied us with sections of the biopsy material. The radiograph in fig. 1 was supplied by Dr. J. J. Stevenson, and reproduced by Miss L. J. Hunt. The photomicrographs were made by Mr. K. G. Moreman. We are indebted to Mr. R. C. Sbresni and Mrs. K. Sosabowska for help with radioactive isotope studies, and to Miss J. Thompson for assisting with the collection of data from the literature. The table is taken from the second Robert Knox memorial lecture (Smithers 1959).

REFERENCES

Ashhurst, A. P. C., White, C. Y. (1925) *J. Amer. med. Ass.* **85**, 1219
Brentano (1911) *Zbl. Chir.* **38**, 498.
Buckman, L. T. (1936) *Laryngoscope*, **46**, 765, 878.
Goetsch, E. (1948) *Ann. Surg.* **127**, 291.
Gunn, L. G. (1910) *Trans. R. Acad. Méd. Ire.* **28**, 381.
Hofer, G. (1920), quoted by Montgomery, M. L. (1936).
Levi, L. M., Hankins, F. D. (1935) *Amer. J. Cancer*, **23**, 328.
Marchal, G., Soulié, P., Grupper, C., Roy, A. (1935) *Bull. Soc. méd. Hôp. Paris*, **51**, 953.
Montgomery, M. L. (1935) *West. J. Surg.* **43**, 661.
— (1936) *ibid.* **44**, 54, 122, 189, 237, 303, 373, 442.
Peracchia, G. C. (1927) *Clin. chir., Milano*, **30**, 209.
Ray, H. M. (1918) *Proc. N. Y. path. Soc.* **18**, 12.
Rutgers, M. (1910) *Ned. Tijdschr. Geneesk.* **1**, 1505.
Seelye, W. K. (1916) *Northw. Med.* **15**, 334.
Smithers D. W. (1959) *J. Fac. Radiol., Lond.* (in the press.)
Tyler, A. F. (1923) *J. Radiol.* **4**, 381.
Wapshaw, H. (1942) *Brit. J. Surg.* **30**, 160.
Watson, W. L., Pool, J. L. (1940) *Surg. Gynec. Obstet.* **70**, 1037.
Willis, R. A. (1953) Pathology of Tumours; p. 609. London.

New Inventions

OPERATING-TABLE FOR HAND SURGERY

HAND surgery demands some device which straightens the fingers and thumb during an operation.

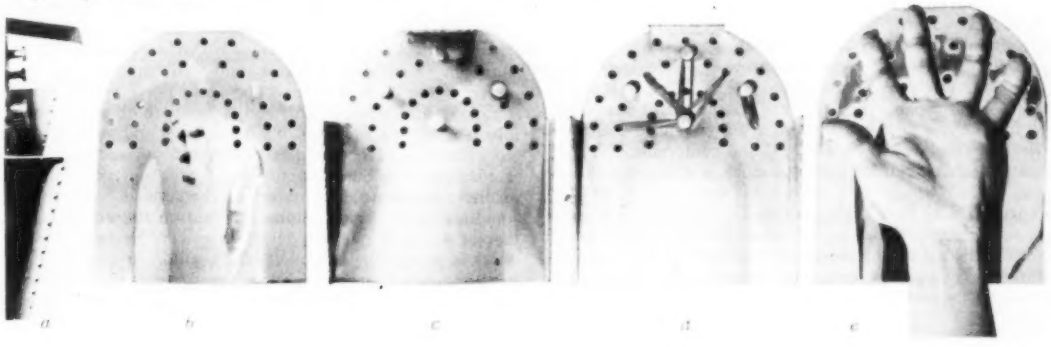
The small operating-table illustrated here has certain advantages over others in current use:

1. The hand is raised a little above the surface of the operating-table, and is set at a convenient angle so that the wrist is not hyperextended
2. Elastic bands enable the fingers and thumb to be flexed and extended during the operation without difficulty.
3. The tension of the elastic bands can be changed easily by altering their position or size.
4. The operating-table can be used for hands of all sizes, including those of small children.
5. It is simple to make and never wears out.

It consists of an inclined plane of metal with multiple $^1/_4$ in. holes, through which rubber bands are threaded. It is made of copper and chromium-plated. There are four capstans on the under surface round which one end of the rubber band is placed; the other end is threaded through the convenient hole and placed round the finger or thumb (figs. a–e).

The table is made by Messrs. Down Bros. and Mayer & Phelps Ltd., Church Path, Mitcham, Surrey.

R. C. HOWARD
F.R.C.S.E.
Norwich



Reviews of Books

Diseases of Children in the Subtropics and Tropics

Editors: H. C. TROWELL, M.D., F.R.C.P., senior specialist physician and lecturer in medicine and pædiatrics, Mulago Hospital and Makerere College, University College of East Africa, Kampala, Uganda; D. B. JELLIFFE, M.D., M.R.C.P., visiting professor of tropical medicine, Tulane University, New Orleans, U.S.A. London: Edward Arnold. 1958. Pp. 935. 105*s*.

THE appearance of this book is a notable event in pædiatrics, for it is the first comprehensive book concerned with the clinical aspects of diseases of children in the subtropics and tropics. It covers only the common diseases, yet it is of necessity a fairly large volume of over 900 pages, for the subject is vast. It is representative of most tropical and subtropical regions, and has no less than 75 contributors from 24 countries.

The varied ethnological and social background against which modern Western pædiatrics is portrayed adds greatly to the interest of the book for pædiatricians everywhere, though much of it must be devoted to diseases peculiar to the tropics. It has been emphasised that backward cultural evolution, causing in turn poverty, malnutrition, and poor public and personal hygiene, is a more important cause of much of the gross disease in childhood, still prevalent in the tropics and subtropics, than are tropical infection and infestation, which are often regarded as the chief menace to good health in these regions. Apart from tropical parasitic diseases much the same picture of widespread gross disease in childhood prevailed in Western Europe a few centuries ago. Many of the numerous illustrations have an interesting social bearing.

This work will assuredly be well received by all concerned in the promotion of child health in the tropics and subtropics. Since the book's publication Dr. Jelliffe has been appointed to the new chair of pædiatrics and child health at Makerere College Medical School, Kampala, Uganda—a chair generously sponsored by the United Nations Children's Fund.[1] This is a fitting compliment to one who had devoted himself wholeheartedly, in both hemispheres, to the development of tropical pædiatrics; and it will ensure that the example of industry and foresight long set in Uganda by Dr. Trowell will be ably followed.

Human Groups

W. J. H. SPROTT, M.A., professor of philosophy, University of Nottingham. London: Penguin Books (Pelican psychology series). 1958. Pp. 219. 3*s*. 6*d*.

The Psychiatric Hospital as a Small Society

WILLIAM CAUDILL, lecturer in social anthropology, Harvard University. Cambridge, Mass.: Harvard University Press (distributed in Great Britain by Oxford University Press): 1958. Pp. 406. 52*s*.

Professor Sprott's admirable little book very ably meets a need. He gives a bird's-eye view of research and opinions concerning what is to many people a very vital subject—the interactions of people within groups, from family via village to neighbourhood, factory, crowd, and even concentration camp. Psychiatric groups are briefly touched upon, and psychoanalytic theory hardly at all, though in its elucidation of group interaction it may find its most important application. (Such an approach by no means conflicts with the sociological aspect; indeed it serves to enrich and illuminate it.) As it is, however, the author has capably digested such a large mass of published work that he was probably right to avoid entanglement in this network of theory. His style is easy and comprehensible, outstandingly so in a subject where so much is ill written at great length.

Penguin Books have again provided a sound scientific summary very cheaply. They do not follow the sometimes irksome practice of listing all the people to whom the book is directed, and indeed it would be very long. Knowledge of how groups work and why they go wrong is important to anyone helping to run institutions, or indeed anyone who is concerned with an occasion where two or three are gathered together—to anyone in fact who takes an intelligent interest in his social environment. When Professor Sprott suggests that all this work adds up to little more than ingenious demonstrations of the obvious, he is being over-modest. It is not obvious to nearly enough people. He is probably right, however, in his suggestion that ". . . the study of the individual personality in isolation from his social environment was appropriate to competitive capitalism . . . the new emphasis on social interaction is appropriate to a society which has become increasingly aware of itself as an interactive system."

With regard to group methods as the Technique of the Future, what the author says (inevitably briefly) about such developments in Russia and China is very interesting. He warns us against expecting magical results in international affairs from the reduction of tension in everyday life. It certainly is a far step from village to summit conference; but the " grass-roots " of politics are surely very important, and perhaps Professor Sprott underestimates the potential contribution of social science to world peace. Applying the work nearer home, it is evident that most of our hospitals are as backward in trying these techniques as are most of our factories—as a means of running things, that is. Therapeutic groups are another matter, and heartening experiments are beginning in some mental hospitals. The general-hospital system remains uncompromisingly feudal.

The impressive book by Dr. Caudill, a young social anthropologist who spent the best part of a year studying open and closed wards in a small American psychiatric hospital, is referred to in an editorial on p. 83. He is an enterprising worker whose previous inquiries (not recorded here) were based on a two-month survey conducted as a patient, unknown to all except the director of the hospital. He ends with a stimulating account of the prospects for anthropology in clinical science. Both books illustrate the great difficulty of codifying human interactions, especially the complicated ones within groups, and it will be a little time before meaningful indices emerge. The subject is still in its early formative phase, and its development will be of wide interest.

A Primer in Medical Technology

P. M. KRAEMER, department of health and hospitals, City and County of Denver, Colorado. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958. Pp. 338. 58*s*. 6*d*.

THIS book is composed of twenty lessons in what in this country is called clinical side-room technique. The author wrote it primarily for those junior technicians who, in the United States, may not have come through the customary educational channels but may have to learn the subject " the hard way " in a small hospital or in the laboratory of a " private physician ". The author also had in mind student nurses, and though the book is written in very simple terms it might benefit the medical student at the beginning of his clinical career, when he should be able to digest it completely in an evening or so. There are four major sections entitled Urinanalysis and Kidney Function, Hematology, Blood Chemistry, and Cerebrospinal Fluid. The first includes an introduction to renal physiology, and the second preliminary considerations of anæmia. The chemical part deals in particular with the evaluation of liver-function tests, with diabetes, and with fluid balance. The scope of the book is limited and there is no mention of bacteriology and parasitology; and, though there are 7 pages on blood-grouping, the work of a blood-bank and serology are not considered. Technical details and tricks of the trade are included, and the book contains much that may be in the minds of most experienced laboratory workers yet is hard to find in the literature. Much emphasis is laid on the development of habits which in one way or another serve to check results as work is proceeding and on efforts to minimise error. Provided that its limited scope is not forgotten, the book can be heartily recommended as a bench guide in the clinical side-room, and it lives up to its title as a primer in medical technology.

1. See *Lancet*, 1958, ii, 1023.

THE LANCET
LONDON 10 JANUARY 1959

Renal Biopsy

FROM a series of a hundred renal biopsies taken at intra-abdominal operation, CASTLEMAN and SMITHWICK [1] showed that in many cases of hypertension (especially the milder ones) there was no appreciable lesion in the kidneys, and thus that hypertension was often not due to such a lesion. At that time, and for some time afterwards, percutaneous renal biopsy was regarded as too dangerous for clinical use.[2] Then IVERSEN and BRUN [3] showed that, with due care, valuable information could be obtained; and KARK and MUEHRCKE [4] introduced modifications, experience with which proved that in reliable hands the method causes few and only minor discomforts and complications. Since then IVERSEN and his colleagues have published over a dozen articles, and KARK and his colleagues over two dozen, describing many instances in which renal biopsy has materially influenced diagnosis, treatment, and prognosis of difficult cases; and the method has also revealed changes in the pathological anatomy of renal diseases at stages not encountered at necropsy. By means of electron microscopy this new technique has greatly widened our knowledge of the normal structure of the glomerulus.[5] ROSS and ROSS [6] admit that renal biopsy has received slow recognition in this country; and they conclude from experience of 26 cases that it is of considerable service in the investigation of renal disease but that its contribution to diagnosis, prognosis, and treatment is limited. WILLIAMS [7] is slightly more enthusiastic but still very cautious about its application in clinical medicine: "renal biopsy affords a means of more precise diagnosis and consequently may influence prognosis and management".

There seem to be two conditions in which all the standard methods of investigation can fail to give a definite diagnosis and in which renal biopsy may materially influence diagnosis and treatment—namely, the nephrotic syndrome and persistent proteinuria. In their first article on renal biopsy [3] IVERSEN and BRUN found an unsuspected renal calcinosis was the cause of the nephrotic syndrome and were able to control hypervitaminosis-D. By biopsy unsuspected amyloid has often been found [8 9] and the cause may be traced; but in some cases the amyloid has been primary. It has been shown too, that in diabetes diffuse glomerulosclerosis is present much more often than the localised form described by KIMMELSTIEL and WILSON.[10] But in this group renal biopsy is especially rewarding where no lesion can be seen in the glomeruli by light microscopy, where the condition has been considered as "lipoid nephrosis", or where there is merely slight thickening of the glomerular basement membrane. Electron microscopy has shown that in lipoid nephrosis in children there is a lesion in the finer detail of the epithelial cells [11]—the foot processes are lost and replaced by a diffuse layer of protoplasm. Similarly in adults,[12] the endothelial cells and basement membrane are normal; but the pedicels are lost, the epithelial-cell cytoplasm is vacuolated, and minute osmiophilic fragments occupy the capsular space. Further, this lesion is reversible: treatment with prednisone causes complete return to normal after diuresis has been established. While these cases have an excellent prognosis, the same cannot be said of those with either proliferative or membranous glomerulonephritis or a mixed lesion: here the prognosis can be based on the extent of the glomerular lesion, but the rate of progress cannot be estimated.

The other type of case where only renal biopsy may be diagnostic is persistent proteinuria where all other investigations give no lead as to the cause. Thus, in five of their first two hundred biopsies KARK et al [13] obtained a positive culture either from the biopsy specimen or from a specimen of urine immediately afterwards, though no positives had been obtained from many previous urine specimens; and by antibiotic treatment an otherwise progressive pyelonephritis was cut short. In some of these positive cases the histological picture was typical of pyelonephritis; but in others the picture was of proliferative glomerulonephritis ("subacute bacterial nephritis"), and under antibiotic treatment this also subsided with little fibrosis. Of other cases of persistent proteinuria with very mild clinical abnormalities,[14] the majority showed various forms of glomerulonephritis, and biopsy helped more in prognosis than in direct treatment; these smouldering forms may possibly be forerunners of the much more severe forms of glomerulonephritis found at necropsy.

In membranous glomerulonephritis electron-micrographs show thickening of the basement membrane and increase of the endothelial cells, whereas in "lipoid nephrosis" these elements are normal and it is the epithelial cells which show changes, with vacuolation of their cytoplasm and loss of the foot processes; yet both sets of lesions (neither connected even indirectly with microorganisms) may produce the same clinical syndrome. It will be interesting to observe the connection, whether complementary or controversial, with the suggested localisation of immune bodies in the basement membrane [15] as seen by light photography, which

1. Castleman, B., Smithwick, R. H. *J. Amer. med. Ass.* 1943, **121**, 1256.
2. Kark, R. M., Muehrcke, R. C., Pollak, V. E., Pirani, C. L., Kiefer, J. H. *Arch. intern. Med.* 1958, **101**, 439.
3. Iversen, P., Brun, C. *Amer. J. Med.* 1951, **11**, 324.
4. Kark, R. M., Muehrcke, R. C. *Lancet*, 1954, i, 1047.
5. *Lancet*, 1957, ii, 1324.
6. Ross, J. H., Ross, I. P. *ibid.* p. 559.
7. Williams, J. D. *Guy's Hosp. Rep.* 1958, **107**, 373.
8. Bjørneboe, M., Brun, C., Gormsen, H., Iversen, P., Raaschou, F. *Acta med. scand.* 1952, **142**, suppl. 266, 233.
9. Kark, R. M., Pirani, C. L., Pollak, V. E., Muehrcke, R. C., Blainey, J. D. *Ann. intern. Med.* 1958, **49**, 751.
10. Kimmelstiel, P., Wilson, C. *Amer. J. Path.* 1936, **12**, 83.
11. Farquhar, M. G., Vernier, R. L., Good, R. A. *ibid.* 1957, **33**, 791. *J. exp. Med.* 1957, **106**, 649.
12. Folli, G., Pollak, V. E., Reid, R. T., Pirani, C. L., Kark, R. M. *J. Lab. clin. Med.* 1957, **50**, 813. *Ann. intern. Med.* 1958, **49**, 775.
13. Kark, R. M., Muehrcke, R. C., Pirani, C. L., Pollak, V. E. *Ann. intern. Med.* 1955, **43**, 807.
14. Pollak, V. E., Pirani, C. L., Muehrcke, R. C., Kark, R. M. *Guy's Hosp. Rep.* 1958, **107**, 333.
15. *Lancet*, 1958, ii, 1215.

includes all three structures—the basement membrane itself, endothelial cells, and epithelial cells.

The research methods of today become the routine of tomorrow. Are there not enough patients in this country with these indefinite syndromes to justify setting up a few units (comprising a team of physician, urologist, pathologist, bacteriologist, and electron-micrographer) to carry out renal biopsies? Is the tardiness in taking up this line due to lack of money, or of opportunity (for instance, no access to electron microscopes), or coordination? Surely it is not due to fatalism in the treatment and prognosis of the commonest forms of the syndromes, or to lack of interest in discovering more about their causes.

Sleep

SLEEP is essential for the wellbeing of both body and mind,[1] yet we know little of its nature. ROBIN [2] has suggested that one reason for our ignorance is that the wrong question has been put: we should ask not "What causes sleep", but "What causes the waking state?" CRUDEN [3] has put forward the notion that sleep is the natural state of man and waking no more than a reaction to possible harmful stimuli. In support of this hypothesis CRUDEN pointed to the long sleeping hours of infants and the aged. But infants are known to be structurally immature for some time after leaving the uterus, which, together with their inexperience, distinctly limits mental activity; for a while, too, muscular coordination is imperfect. Thus their energies are directed towards development and growth. The premature infant becomes as active as the full-time one only when it reaches a comparable stage in development. At the other end of life, in the old man, certain forms of nervous reactivity [4] are reduced; his endocrine system and circulation are not what they were, and he fatigues easily; so he takes little naps. But in healthy old people the total sleep time is not usually greater, and is often less, than that of young or middle-aged adults. CRUDEN classed hunger and desire as potentially injurious stimuli, which broke sleep until satisfaction was obtained. Against this, a series of small meals prevents hunger without inducing slumber, and desire and its satisfaction so violently stimulate both nervous and endocrine systems that the sequential and often brief sleep is perhaps better thought of as restorative. It has to be remembered, too, that joyful anticipation can keep us wakeful, and that profound sleep may be a happy way of delaying an unpleasant decision. It has even been suggested that hungry children sleep more quietly than full-fed ones [1 2]; and that when aroused we stay awake is attributed to wake maintainers of unknown nature.

Study of the lower forms of animal life does not help us. Forms such as fish and earthworms have periods of quiescence, but it is not known whether these are comparable with sleep. This interesting and in some ways stimulating suggestion—that sleep is life and waking no more than a guard against loss of sleep—is not acceptable unless the definition of life is altered. Living creatures not only metabolise but move, take in nourishment, and reproduce. Metabolism and movement occur in sleep, but not eating or reproduction. Waking is necessary for sleeping as sleeping is for waking; and life, as defined, could not endure for the individual or the species in the absence of the waking state. Thus, we need to ask the causes of both states and the reason for the alternating rhythm.

The problem of sleeping and waking can be approached in two ways: by a direct investigation of the factors leading to, or modifying, one or the other; or by an indirect method in which the physiology of the organism in the two states is compared. The latter method may tell us why sleep is necessary, what happens in sleep apart from loss of consciousness, and thus the means by which one or other state may be attained. The observational method was used by LEWIS and MASTERTON [5] during two years spent in the Arctic, where they studied the effect on sleeping-time of long daylight and long darkness, and of sleeping on demand. In their isolation most of the men could sleep when they wished and for as long as they wished, since the only compulsion was to perform tasks which could be finished fairly quickly. It was found that the total sleep-time per month was the same as in more usual circumstances, though its distribution in the day differed with the seasons. Sleep-time was slightly but significantly longer in autumn and shorter in spring. Despite the freedom to sleep at will, the hours taken were the same in winter as in summer, although there was more work to be done in the warmer season. LEWIS and MASTERTON concluded that the conventional eight hours of sleep may represent a biological need uninfluenced by light and darkness, work, or social pressure. By the direct experimental approach, HESS [6] showed as long ago as 1931 that, according to the site, electrical stimulation of the diencephalon could lead to a condition in every way resembling sleep, or could induce waking. Since then MAGOUN [7 8] has found that the reticular formation—an elongated central area lying in the mesencephalon—is importantly related to sleeping and waking. The mesencephalon is a richly interlacing network of nerve-cells and their processes which receives collaterals from the auditory and all peripheral modalities; this system projects to the cerebral cortex, and in return receives fibres from all parts of the cortex except the visual region. Such a linking structure suggests an intricate coordinating system. That the reticular formation receives information from the periphery is certain; for electrodes lying in it can record potential changes in response to touch or clicking sounds [7]—types of stimulation which could wake a sleeping person. Nevertheless, in the absence of all sensory stimuli, on electrical stimulation of the arousal area the electroencephalographic (E.E.G.) changes from the sleeping to the waking pattern and behaviour is that of arousal—in other words, the subject

1. Laslett, H. R. *J. exp. Psychol.* 1928, **11**, 370.
2. Robin, E. D. *Arch. intern. Med.* 1958, **102**, 669.
3. Cruden, W. V. *Lancet*, 1957, i, 579.
4. Gellhorn, E. Autonomic Imbalance and the Hypothalmus. Minneapolis, 1957.
5. Lewis, H. W., Masterton, J. P. *Lancet*, 1957, i, 1262.
6. Hess, W. R. *C. R. Soc. Biol., Paris*, 1931, **107**, 1333.
7. Magoun, H. W. *Arch. Neurol. Psychiat.* 1952, **67**, 145.
8. Magoun, H. W. The Waking Brain. Springfield, Ill., 1958.

wake up. Moreover, such stimulation induces no spurious feeling of having had a sensory experience.[9] Wakefulness outlasts the duration of the stimulus which induces it.[7] Lesions in the arousal area produce sleep.[7]

It is pertinent to ask the fate of sensory stimuli. As ADRIAN [10] expressed it: "Do messages find the brain asleep, awake and preoccupied, or awake and ready to receive them? Do messages always reach the cortex even in sleep and coma?" E.E.G. records taken during sleep [9] showed arousal bursts when verbal commands were given, even though the commands were not obeyed because the subject was too deeply asleep. Even in a state of faint, words of command changed the E.E.G. pattern and led to incomplete arousal in the total absence of perception or recollection. Thus in unconsciousness stimuli still reach the cerebral cortex but are ineffective. This dampening of response is in some way related to reticular-formation activity, which either raises or lowers levels of cortical activity or actually modifies the organisation: that is, it may wake us and send us to sleep, or it may have something to do with the direction of attention—the actual work of the conscious brain.[11] More cannot be said in our present ignorance. We need to know many more facts.

The facts that are already known include some showing the complex changes on transfer from the waking to the sleeping state. Consciousness and somatic muscular activity are minimal in some animals, though some, like the horse, sleep when standing; other activities persist—for instance, gastric contractions occur, sphincters remain closed, the eyes are actively shut, the pupil is small. Both day and night sleep reduce the heart-rate, and after two hours of sleep the blood-pressure may be 26–21 mm. Hg below the waking level [12]; the basal metabolic rate is reduced. There is a rise in alveolar CO_2 tension which is reflected in general acidosis. Tendon reflexes are absent or diminished. In health the volume of urine formed in sleep is small; which is in complete contrast to the waking renal response to assumption of the horizontal position. On lying down, in wakefulness the redistribution of blood from the lower limbs to the thorax initiates a prompt reflex inhibition of release of antidiuretic hormone, and there is also a slow increase in blood-volume owing to reabsorption of fluid accumulated in the intercellular spaces of the lower limbs. Both these factors bring about an increase in urinary volume. In sleep these responses to lying down are suppressed by modification of central nervous activity.

The changes in physiological activity in sleep merit attention. It has rightly been pointed out that respiratory modifications which are proper and harmless in health are not necessarily so in disease.[2] For instance, in chronic pulmonary disorders such as emphysema, even during waking hours the patient has some diminution of arterial O_2 saturation and a higher than normal CO_2 tension, with slight depression of the respiratory centre. When during sleep both the O_2 desaturation and the increase of CO_2 tension are exaggerated, the resulting hypoxia is considerable; and it is not surprising that these patients are particularly uncomfortable soon after waking. Again, the redistribution of blood and increase in blood-volume on assumption of the horizontal position causes no inconvenience to the healthy person; but where there is left ventricular weakness the result may be pulmonary congestion and œdema and the onset of a paroxysm of dyspnœa. Where treatment is concerned, the rhythmical variation in activity of some of the endocrine glands may be important. The excretion-rate of hydrocortisone, in both day and night workers, is greatest between midnight and 9 A.M., suggesting that this is the time of greatest activity for the adrenal gland. If this is indeed the case, it bears on the timing of doses of adrenal steroids. A small dose of steroid given early in the morning will minimally suppress the spontaneous activity of the gland and maximally add to the endogenous-hormone supply. Another point of interest is the curious relation between host and parasite. It has been noted that the microfilariæ of *Wuchereria bancrofti* are most easily found in the blood during sleep, whether during the day or night: in the waking state the embryos disappear from the peripheral circulation. So far the cause of the filarial periodicity is unknown.

There is a great deal to be discovered about sleep. When it fails us, old remedies still have their use: quiet, darkness, relaxation, and warmth—that is, conditioned stimuli which may bring about the wished-for conditioned response. If these, too, fail, there are a host of remedies both old and new, from hot milk or hot whisky to a great and growing range of drugs.

9. Jung, R. *in* Brain Mechanisms and Consciousness (edited by J. F. Delafresnaye). Oxford, 1954.
10. Adrian, E. D. *ibid.*
11. Hebb, D. O. *ibid.*
12. Kleitman, N. *Physiol. Rev.* 1929, **9**, 624.

Annotations

SOCIOLOGY AND THE MENTAL HOSPITAL

THE importance of studying the psychiatric hospital as an institution was demonstrated by the famous work of Stanton and Schwartz.[1] They showed that in such a society collective disturbances on the ward could be related to tensions among the higher grades of medical staff, and they showed, too, how readily tensions were built up within this system of "blocked mobility", wherein promotion between the various groups—patient, orderly, nurse, ancillary staff, lay administrator, and doctor—was virtually impossible. It became clear that forces other than medication and individual psychotherapy were bearing on the patients' recovery or relapse, and that much more attention must be turned to the "other 23 hours" when the patient was not seeing his doctor. There followed an upsurge of interest in this subject which was reflected in much published work, some of it in our own columns.

The latest satellite dispatched from the corpus of sociology to report back about psychiatric outer space is Dr. William Caudill, a social anthropologist, whose important book is noted in our review columns this week. From his inquiries he is able to confirm the findings of Stanton and Schwartz regarding collective disturbances, and he shows how role, status, and group-influence among

1. Stanton, A. H., Schwartz, M. S. The Mental Hospital, New York, 1954. See *Lancet*, 1955, ii, 379.

patients in a small psychiatric hospital affect an illness. The ability of a person to fill his relatively passive patient-role and to do well in hospital does not necessarily indicate that he would do well outside. Caudill used a special picture-interview technique, modelled on the thematic apperception test, to assess the ideas which patients and certain staff had about their own roles and those of others, and he demonstrated a similarity between the structure of hospital roles and those in the family. Staff need to be aware of their relationships with each other and to examine their motivations towards the patients; and Caudill believes that, for a truly therapeutic community to emerge, drastic changes in structure are needed, and much retraining of staff. He suggests that one way out of the tight vertical structure would be to encourage what he calls " lateral echeloning "—permitting doctors to undertake extramural activities and patients to go out to work, for instance. At staff conferences administrative problems caused more trouble than therapeutic ones, and the two functions, Caudill holds, are best handled separately, though exceptionally a doctor may be able to deal with patients satisfactorily in both respects. Detailed examination of these conferences indicated that a person's verbosity corresponded precisely with his place in the hierarchy. The senior doctors talked more than the juniors, but the quietest junior still spoke more than the brightest sister, and so on down. Each person's loquacity remained very constant throughout the 63 daily conferences studied, and it was noted that the seniors' estimates of their subordinates' capabilities correlated precisely with the amount they said—a finding that may surprise some readers.

The familiar inference from these further observations is that we must become more aware of the world in which we work and of what goes on underneath and in those " other 23 hours "—whether in mental or in other hospitals. We are indebted to the United States for much of our knowledge of this subject, but this country also has made some notable contributions, such as those by Maxwell Jones [2 3] and his colleagues at Belmont Hospital and by Clark.[4] The wise use of group methods will probably be the logical answer to the problems raised by Caudill, though he does not mention this possibility.

PHENACETIN NEPHROPATHY

As far back as 1953 phenacetin was added to the list of drugs with nephrotoxic properties. Consumption of large amounts, of the order of 2 or 3 g. a day, for many years may impair renal function and lead to incipient uræmia and a clinical picture similar to that of chronic pyelonephritis. Necropsy findings [5] of " primary chronic interstitial nephritis " in phenacetin poisoning drew attention to the possible effects of chronic phenacetin abuse.

In Denmark the phenacetin habit is common among women and the possibility of chronic phenacetin poisoning is now prominent in the minds of Danish physicians. The first signs are often those of methæmoglobinæmia, and subsequently the patient is found to have proteinuria, hyposthenuria, or other signs of nephropathy. Renal symptoms may be the presenting feature but are often mild. Lindeneg [6] found a close correlation between chronic phenacetin habituation, usually taken for headache or nervous symptoms, and chronic renal impairment, confirmed by renal function tests, necropsy studies, and renal biopsies. Although the renal damage might have other origin in some cases, particularly when infection is a factor, this is unlikely to be so in the majority of Lindeneg's cases. The common finding of renal papillary necrosis seems very important because this syndrome is on the increase in Denmark.[7] Phenacetin may be an unsuspected cause or aggravating influence in some chronic renal diseases.

The combined effects of advertising and neurosis may produce more chronic phenacetin abuse in this country, and its possible effects must be kept in mind, particularly since they tend to produce no symptoms for a long time, yet may end in death. Perhaps mixtures of analgesics should be carefully chosen if they are to be used for long periods or for patients with renal disease. In Britain aspirin has been a popular analgesic, and this may have lessened chronic phenacetin poisoning; but it seems likely that if phenacetin abusers were investigated nephropathy would be found in some of them, and if patients with chronic pyelonephritis were questioned about phenacetin intake some of the answers might be revealing.

TRACHEAL FENESTRATION FOR THE RESPIRATORY CRIPPLE

In patients with chronic respiratory disease much disability is often caused by purulent secretions in the respiratory tract. Usually antibiotic therapy and postural drainage bring relief, but occasionally it is necessary to suck out the secretions with a catheter introduced into the bronchial tree by means of bronchoscopy or tracheostomy. Hitherto direct bronchial toilet has been regarded as a temporary expedient useful for tiding the patient over an acute exacerbation; but Rockey et al.[8] now report that by a new technique—tracheal fenestration—it can be used for much longer periods.

Tracheal fenestration consists in exposing the trachea through a transverse incision in the neck, incising a square from its anterior wall, and covering the window so created with two skin flaps arranged in such a way that they normally occlude it completely, but nevertheless permit the insinuation of a catheter into the trachea as required. Since the tracheal opening is completely closed by the skin flaps unless they are specially manipulated, the patient is able to phonate. Secretion is aspirated by passing catheters between the skin flaps into the tracheobronchial tree; six to eight catheters of various sizes and shapes are inserted at each session, and patients are taught to do this for themselves. Rockey et al. claim that patients easily learn to pass a catheter at will into the right or left bronchial tree, and that some even learn to catheterise individual lobar bronchi.

Four patients crippled by emphysema who were treated by tracheal fenestration were observed over a considerable period. Two of these patients, who had been producing abundant purulent sputum, were greatly benefited; and so, surprisingly, were two who had been producing no sputum at all. Suction in the " dry " cases yielded a little grey, viscid, doughy secretion similar to that obtained in the " wet " cases after cleaning up by repeated aspiration. Since breath sounds became audible in the " dry " cases soon after secretion had been sucked out, Rockey et al. suggest that in the emphysematous airway blockage is a

2. Jones, M. Social Psychiatry. London, 1953.
3. Jones, M., Rapaport, R. M. *Lancet*, 1955, ii, 357.
4. Clark, D. H. *ibid.* 1958, i, 805.
5. Spuhler, O., Zollinfoe, H. U. *Z. klin. Med.* 1953, **151**, 1.
6. Lindeneg, O. *in* Phenacetin Poisoning and Renal Disease. Festschrift for Dr. N. I. Nissen, Frederiksberg Hospital, Copenhagen.
7. Schourup, K. *Acta path. microbiol. scand.* 1957, **41**, 462.
8. Rockey, E. E., Thompson, S. A., Blazsik, C. F., Ahn, K. J. *N.Y. St. J. Med.* 1958, **58**, 3607.

more important source of disability than bronchospasm. Two patients died after gaining temporary benefit, but the respiratory function of the other two improved so much that they were able to go home and engage in normal activities. On discharge from hospital they were supplied with sets of catheters and a suction apparatus so that they could continue to carry out bronchial toilet as outpatients. One of these patients had "dry" emphysema and needed two aspiration sessions daily; the other had "wet" emphysema and needed four or five. Rockey et al. report excellent results in two further cases of emphysema treated in this way but observed for a shorter period.

They consider that tracheal fenestration is indicated in advanced cases of emphysema with or without suppuration, in other suppurative pulmonary disease in which surgery is contraindicated, and in cases of poliomyelitis where permanent mechanical ventilatory assistance is required. More experience is obviously needed before the value of this technique in chronic respiratory disease can be properly assessed, but it is certainly a bold and ingenious attempt to bring relief to the respiratory cripple.

RADIATION-INDUCED MUTATIONS

ONE of the important assumptions that has been made in trying to measure the genetic effects of ionising radiations is that the number of radiation-induced mutations depends solely on the total dose delivered and in no way on the dose-rate. This hypothesis, based largely on experiments with the fruitfly, drosophila, is beginning to look decidedly shaky.

Observations on drosophila spermatozoa are of uncertain value when it comes to deciding what happens in man, in whom most of the radiation dose liable to do genetic harm is experienced not by spermatozoa but by the less mature spermatogonia and the oocytes; and Russell and his colleagues at Oak Ridge, Tennessee, have sought to settle this vital question by determining mutation-rates induced by chronic γ-irradiation in spermatogonia of mice and comparing them with the results of "acute" doses of X rays. First results [1] showed that, contrary to the well-established hypothesis, the mutation-rate after chronic γ-irradiation was much lower than that induced by exposure at high dose-rate. Some of the questions that immediately arose were whether this difference was attributable to intensity or to quality of radiation, and whether the mutation process itself was affected or whether some secondary change was involved, possibly cell selection due to damage to the seminiferous epithelium. New data [2] from Oak Ridge now confirm that chronic γ-radiation is significantly less effective than acute X-radiation in inducing specific locus mutations in mice spermatogonia. Russell et al. report that this lower mutation-rate was due mainly to difference in dose-rate rather than to any change in the quality of the radiation: acute γ-radiation from a ^{60}Co source had much the same mutagenic action as acute X rays. A dose-rate effect was *not* observed in experiments with mouse spermatozoa, in accord with earlier findings, and some characteristic of the gametogenic stage probably determines the intensity dependence of spermatogonia. One of the most striking of Russell et al.'s observations is that dose-rate was genetically significant in oocytes as well as in spermatogonia; and the inference is that it is the mutation process itself which is influenced by dose-rate, since cell selection, which might account for the radiation effects in spermatogonia, is unlikely to operate for oocytes. An intensity effect does not necessarily imply that there is always a threshold for induced mutations in spermatogonia and oocytes, but that is a possibility.

If dose-rate matters, the genetic impact of medical X rays is likely to be much greater than that of background radiation, for example; but before confident comparisons can be made more must be learnt about both high and low dose-rates. In Russell et al.'s experiments the acute X rays were delivered at a rate of 80–90r per minute. It is quite usual in intravenous pyelography, for instance, to give a gonad dose of 3r during an exposure of 0·6 second—a dose-rate of 300r per minute. Still higher rates are common in diagnostic radiology, and presumably the frequency of genetic changes at such rates will not necessarily follow the pattern of 80–90r per minute.

In this country Carter and his colleagues [3 4] have also made notable contributions to the understanding of radiation-induced mutations in mice. A study [3] of adult female and fœtal male mice suggested two possibilities: that there is a dose-rate effect which operates in non-mitotic material and makes an acute X-ray dose more mutagenic than a chronic γ-ray dose; or that adult male spermatogonia are more mutable by irradiation than adult female oocytes. The second possibility is clearly relevant to the prevention of genetic damage by medical radiology, for it might mean that the protection that is easiest to provide—namely, shielding of male gonads—would also be the most effective. But, as Carter emphasises, the relationships observed in mice cannot be assumed in man, though man is likely to resemble the mouse more than the fruitfly. The Oak Ridge work, on the other hand, produced no evidence of a striking contrast between oocytes and spermatogonia in sensitivity to mutation induction, and it does not therefore favour the view that a difference in genetic effect can be attributed to sex difference. But this and several other key issues can hardly be taken as settled, and only very large experiments are likely to deliver a firm answer. The next step seems to be a genetic study with lower dose-rates, and that will mean great numbers of animals and enormous labour.

NEW YEAR HONOURS

THE knighthood conferred on Prof. A. P. Thomson will please both those who know him and those who have read him. For he has a freshness of mind which has never been dimmed by his strenuous years as physician, teacher, and administrator at Birmingham; and the seriousness of his purpose goes with an engaging lightness of heart as well as an astringent wit. Some of his work for old people and the chronic sick was summarised memorably in his Lumleian lectures for 1949,[5] and some of his medical philosophy in his presidential address to the British Medical Association last July.[6]

The two other medical knights belong to other nations of the Commonwealth. Dr. M. A. S. Margai, who graduated at Durham in 1926, is Premier of Sierra Leone. Dr. A. W. Morrow, of Sydney, has won respect alike by his war services, by his work as a physician, and by his quiet influence in the counsels of our profession. To these colleagues, and to the others named on p. 90, we offer warm congratulations.

1. Russell, W. L., Kelly, E. M. *Science*, 1958, **127**, 1062.
2. Russell, W. L., Russell, L. B., Kelly, E. M. *ibid.* 1958, **128**, 1546.
3. Carter, T. C. *Brit. J. Radiol.* 1958, **31**, 407. See *Lancet*, 1958, ii, 1218; *ibid.* p. 1317.
4. Carter, T. C., Lyon, M. F., Phillips, R. J. S. *Nature, Lond.* 1958, **182**, 409.
5. *Brit. med. J.* 1949, ii, 243, 300.
6. *ibid.* 1958, ii, 119.

Special Articles

RESULTS OF TREATMENT OF CARCINOMA OF THE BREAST

DIANA BRINKLEY
M.B. Lond., D.M.R.T.
ASSISTANT IN CLINICAL RESEARCH TO THE REGIUS PROFESSOR OF PHYSIC, UNIVERSITY OF CAMBRIDGE

J. L. HAYBITTLE
M.A. Cantab.
PRINCIPAL PHYSICIST, RADIOTHERAPEUTIC CENTRE, ADDENBROOKE'S HOSPITAL, CAMBRIDGE

THE area served by the Radiotherapeutic Centre, Addenbrooke's Hospital, is largely rural but includes, in addition to Cambridge, the towns of Stamford and Peterborough to the north-west, Wisbech and King's Lynn to the north, Newmarket and Bury St. Edmunds to the east, and Huntingdon to the west. The hospitals outside Cambridge are under the control of the East Anglian Regional Hospital Board and are referred to in this paper as the regional hospitals. We report here the results of treatment of new cases of carcinoma of the breast drawn from this area and first treated during the years 1947–50.

Material

All patients referred to the centre have been included. In addition, we have collected other cases from the general records department of the hospital, and have checked through the theatre operation lists at Addenbrooke's Hospital and at the local nursing-homes. The surgeons in Cambridge have also made available the records of their private patients. We believe, therefore, that we have complete figures on new cases of carcinoma of the breast in Cambridge and its immediate neighbourhood.

Owing to the inadequacy of hospital records, it has only been possible to include patients from the rest of the area who were actually referred to this department. During the period studied, the surgeons at the regional hospitals did not refer all operable cases for postoperative irradiation; and some indication of the extent of the omission in operable cases is shown in table I by the lower proportions of patients referred from the regional hospitals receiving surgery only. There were also, no doubt, some late stage-IV cases who were considered too advanced for any treatment.

It was possible, with the aid of the surgeons, general practitioners, National Health Service executive council officers, and officials of Somerset House, to trace up to Sept. 30, 1957, all the 705 new cases of carcinoma of the female breast seen during the period under review. At least a seven-year follow-up is, therefore, available.

Method

Staging

For the purpose of analysis, we have used the following system of staging:

Stage I.—The growth is confined to the breast without involvement of skin or the pectoral muscle. Tethering or dimpling of the skin over the lesion and or nipple retraction do not affect the staging.

Stage II.—As stage I, but with palpable, mobile nodes in the axilla of the same side.

TABLE I—DISTRIBUTION OF OPERABLE CASES BETWEEN CAMBRIDGE HOSPITALS AND OTHER HOSPITALS IN THE REGION

	Stage			Unstaged
	I	II	III	
Other hospitals:				
No. of cases	77	79	47	97
% having surgery only	22	4	15	23
Cambridge hospitals:				
No. of cases	60	53	34	10
% having surgery only	52	40	38	30

Stage III.—The disease is locally advanced, as shown by any or all of the following signs: skin involvement with or without ulceration, *peau d'orange*, and fascia or muscle infiltration. Mobile axillary nodes may or may not be palpable.

Stage IV.—The disease has extended beyond the breast area as shown by: (1) fixing or matting of axillary glands; (2) secondary deposits in the supraclavicular nodes; (3) secondary deposits in the skin wide of the lesion; (4) secondary deposits in the opposite breast; (5) distant metastases (e.g., bones, liver, lung).

This staging is similar to that used at the Christie Hospital and Holt Radium Institute in Manchester and cited by Smithers et al. (1952), but differs in one particular—namely, that any involvement of the skin places the case in stage III.

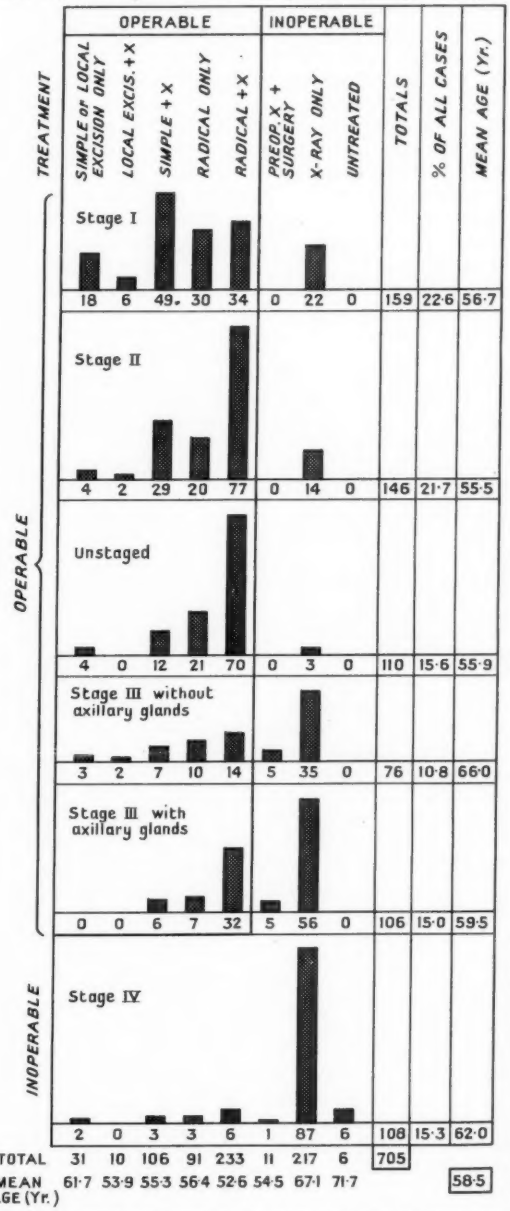

TREATMENT
OPERABLE
INOPERABLE
SIMPLE or LOCAL EXCISION ONLY
LOCAL EXCIS. + X
SIMPLE + X
RADICAL ONLY
RADICAL + X
PREOP X + SURGERY
X-RAY ONLY
UNTREATED
TOTALS
% OF ALL CASES
MEAN AGE (Yr.)
Stage I
18 6 49 30 34 0 22 0 159 22·6 56·7
Stage II
4 2 29 20 77 0 14 0 146 21·7 55·5
Unstaged
4 0 12 21 70 0 3 0 110 15·6 55·9
Stage III without axillary glands
3 2 7 10 14 5 35 0 76 10·8 66·0
Stage III with axillary glands
0 0 6 7 32 5 56 0 106 15·0 59·5
Stage IV
2 0 3 3 6 1 87 6 108 15·3 62·0
TOTAL 31 10 106 91 233 11 217 6 705
MEAN AGE (Yr.) 61·7 53·9 55·3 56·4 52·6 54·5 67·1 71·7 58·5

Fig. 1—Distribution of patients by stage and type of treatment. Figures show numbers of patients in each subgroup and mean ages of main groups. The division according to operability is also shown.

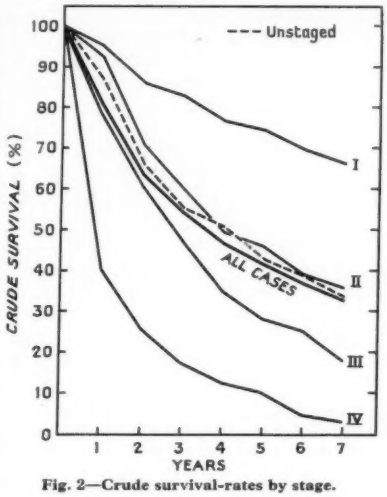


Fig. 2—Crude survival-rates by stage.

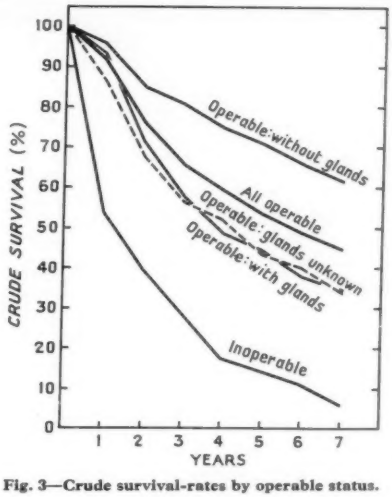


Fig. 3—Crude survival-rates by operable status.

In the staging of Smithers et al. involvement of the skin is allowed in stage I, provided " that the area involved is small in relation to the size of the breast ".

We have made this modification partly because the extent of skin involvement in relation to the size of the breast was not always recorded, and also because the estimation of whether such involvement is relatively small introduces a factor which may vary greatly from one observer to another. The possible effect of this modification would be to cause an apparent improvement of our results in both stage I and stage III, compared with those reported by centres using the Manchester staging.

The staging has been done on the preoperative clinical findings or the pre-treatment findings in those who did not undergo operation. Where the clinical findings before radical mastectomy were unobtainable or incomplete, we have left the case as unstaged. Most such cases were operated on in the regional hospitals (see table I). In cases where simple mastectomy was done and the preoperative information was unobtainable, the decision as to whether a case was placed in stage I or stage II was made according to the state of the axillary glands at the time the patient was referred for X-ray treatment.

Treatment Policy

This survey has been done in retrospect, and during the period there was no fixed treatment policy for carcinoma of the breast. All operable cases underwent operation, but whether they had a radical or simple mastectomy was at the discretion of their surgeon. The use of simple mastectomy was more common with the surgeons attached to the regional hospitals.

In 1947 postoperative irradiation was usually applied in two adjacent direct pectoral fields 15 × 10 cm. each, plus anterior and posterior opposing axillary fields, 15 × 15 cm. each. 220 kVp X rays, h.v.l, 1·5 mm. Cu. were used to deliver a minimum tumour dose to both regions of 2700r in an overall time of eight days.

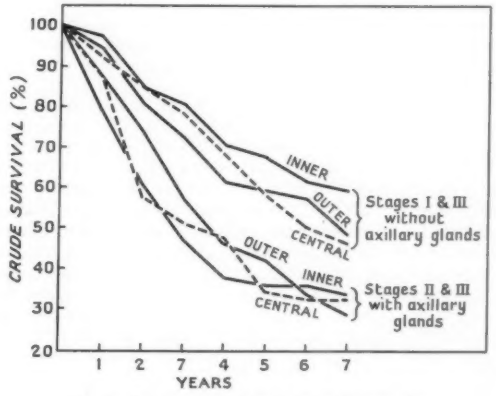


Fig. 5—Crude survival-rates according to site.

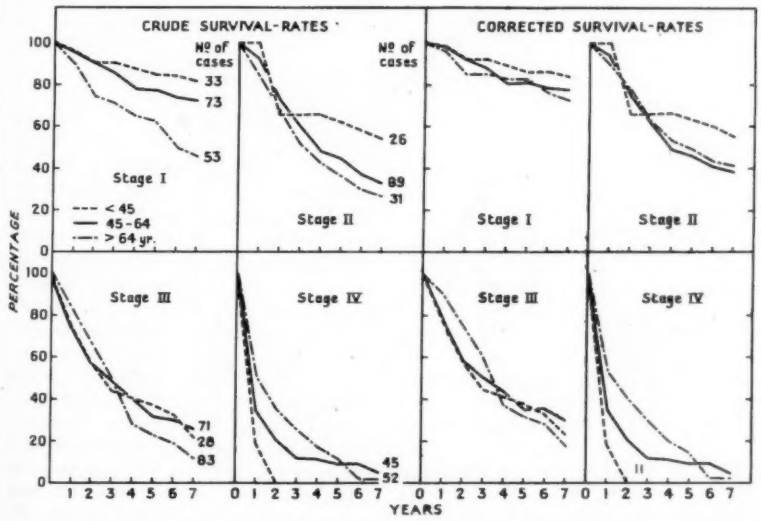


Fig. 4—Crude and corrected survival-rates in the four stages divided into three age-groups.

It was found that a relatively high incidence of lung fibrosis resulted using this technique, and, as a consequence, it was decided to irradiate the pectoral area by two opposing glancing fields, 15 × 15 cm. each. This change took place during the period under review so that by 1950 the most common treatment was by the glancing-field method. The axillary fields, dosage, and overall time remained the same. Inoperable cases and later recurrences were treated palliatively with X rays and with hormones.

Fig. 1 shows the way in which the cases were distributed between the clinical stages and also between the different methods of treatment. Cases have been grouped according to the initial type of treatment given, and no account has been taken of subsequent treatment of recurrences. A patient was considered to have been treated by

TABLE II—COMPARISON OF TREATMENT METHODS: CAMBRIDGE 1947–50

—	Stage I															Stage II								
	State at:															State at:								
	2 years					5 years					7 years					2 years			5 years			7 years		
	Simple + X	Radical + X	Radical only	All simple	All radical	Simple + X	Radical + X	Radical only	All simple	All radical	Simple + X	Radical + X	Radical only	All simple	All radical	Simple + X	Radical + X	Radical only	Simple + X	Radical + X	Radical only	Simple + X	Radical + X	Radical only
Mean age (yr.)	54·5	48·0	56·5	56·8	52·0	..	..	..	..	..	..	..	..	..	..	55·3	53·6	52·2	..	..	..	..	..	..
Total no. of patients	49	34	30	73	64	49	34	30	73	64	49	34	30	73	64	29	77	20	29	77	20	29	77	20
Dead with cancer	2	2	3	4	7	4	7	8	8	15	8	7	9	14	16	4	23	5	8	44	12	14	49	13
No. recurred	6	7	5	12	12	10	9	11	22	20	11	11	11	26	22	7	39	8	11	49	14	18	51	14
Died from intercurrent disease cancer-free	1	1	0	4	1	3	1	1	6	2	4	1	3	7	4	2	0	0	2	1	1	4	1	1
Crude survival-rate (%) ..	94	91	90	88	88	86	77	70	79	73	76	77	60	70	69	79	70	75	66	42	35	38	35	30
Crude recurrence-free rate (%)	86	77	83	78	80	74	71	60	62	66	69	65	53	55	59	69	49	60	55	35	25	24	32	25
Net survival-rate (%) ..	96	94	90	94	89	91	79	73	88	76	82	79	67	79	73	85	70	75	70	42	37	44	36	32
Net recurrence-free rate (%)	88	79	83	83	81	78	73	62	67	68	76	67	59	61	63	74	49	60	59	36	26	28	33	26
Difference between net recurrence-free rates simple + X and radical + X																25 ± 10·2			23 ± 11·0					

surgery and radiation combined if the interval between the two treatments was not more than six months. An interval approaching this length was exceptional, surgery usually being followed by radiation within a month.

Surgery was classed as radical if it included removal of the whole breast and pectoral muscles together with axillary dissection. Simple mastectomy was taken to mean removal of the breast either with or without the excision of easily accessible axillary glands.

Fig. 1 also makes clear some of the factors influencing the choice of treatment. In stage-I cases simple mastectomy or local excision was rather more favoured than the radical operation.

In stage-II cases, by contrast, the surgeons were evidently much less prepared to put their faith in anything less than radical surgery. Most of the unstaged group were treated by radical mastectomy with or without irradiation, and the reason for the cases being unstaged was nearly always lack of information as to the clinical state of the axillary glands before operation. In the unstaged group the distribution between treatments and the mean age are very similar to those of the stage-II cases. This, taken in conjunction with the survival-rates given below, suggests that the majority of the unstaged cases were, in fact, stage II.

Most cases in stages III and IV were treated by X rays only. Age and general conditions prevented the use of surgery in a few cases in earlier stages. It is worth noting that the X-ray-only group and the 6 untreated patients had the highest mean ages. The mean ages of stages III and IV were higher than those of stages I and II and the unstaged cases.

A less satisfactory classification is into two classes designated as "operable" and "inoperable". We feel that the fairest way of fixing this division in our cases is to class as operable all those other than in stage IV who were, in fact, operated on as the primary treatment—i.e., the "inoperable" group were all stage-IV cases and those in other stages treated by X rays only or by preoperative X rays plus surgery. The division, made clear in fig. 1, results in an operable group of 457—i.e., 65% of all patients.

Findings

Crude Survival-rates

The crude survival-rates over the seven-year period are shown in fig. 2. The overall five-year survival-rate for all cases was 41%, and the results are comparable with those reported by other workers for relatively unselected groups of patients (Smithers et al. 1952, McWhirter 1955, Bond 1957).

Fig. 3 shows the crude survival-rates of our cases divided according to operable status. It will be seen that the curve for the unstaged cases in which the state of the axillary glands was unknown follows very closely the curve for the operable cases with clinically involved axillary glands. The five-year rate was 56·7% for the staged operable cases, in 50·6% of whom axillary nodes were involved. The rate was 53·2% for the whole operable group, of which (assuming the unstaged cases had involved nodes) 62·2% had involved axillary glands.

Age

The effect of age on prognosis in our series is illustrated in fig. 4 where the crude survival-rates are plotted by stage and age-group, and are compared with the survival-rates corrected for deaths from other causes by the method suggested by Berkson (1942). Except in stage IV the crude survival-rates tend to decrease with increasing age; but the effect of age on corrected rates is small, although there is some suggestion that patients under 45 years of age have a slightly better prognosis in stages I and II.

Site

Our results in stages I, II, and III, divided according to site, are shown in fig. 5. Cases in which the whole breast was involved, or the site was unknown, have been excluded. The rates for each site do not differ significantly, and the picture remains the same if the stage-III cases are omitted.

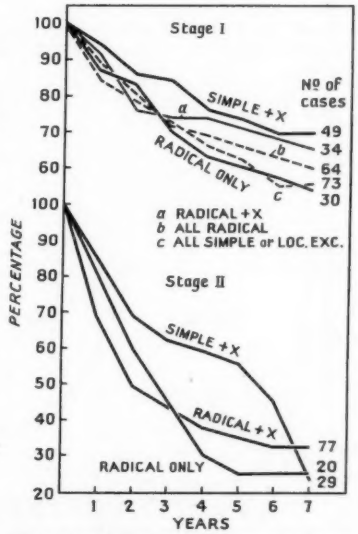


Fig. 6—Crude recurrence-free rates in stages I and II according to type of treatment.

Method of Treatment

The majority of patients in stages I and II were treated by one of three methods—simple mastectomy followed by irradiation, radical mastectomy followed by irradiation, or radical mastectomy alone. The relevant survival data for these patients at two, five, and seven years are given in table II.

In stage I the figures are also given for all patients who had simple mastectomy or local excision with or without postoperative X rays and for the two radical groups combined.

Considering first the stage-I cases only, we see that at two and seven years the survival-rates in the two groups with postoperative irradiation are similar; and, although at five years the rates for the simple-mastectomy group are higher, the differences are not statistically significant at the 5% level. The radical-only group has lower survival-rates at five and seven years, but again the differences are not sufficient to justify any firm conclusions about the effect of postoperative irradiation on prognosis. It should be noted that the patients having the radical operation followed by X rays tended to be younger; 16 out of 34 were under 45 years of age. But the calculation of corrected rates, and also restriction of the comparison to patients aged 45 and over, do not alter the above picture.

For stage-II cases the survival-rates of the simple + X (i.e., plus X rays) group are higher than those for the radical + X patients, and at five years the differences are statistically significant at the 5% level. Further light is thrown on this by examination of the recurrence-free rates, which are plotted for the whole seven years in fig. 6. This shows a sharp drop in the radical + X curve during the first two years, similar recurrence-rates *per year* between two and five years, and a greater incidence of recurrence in the simple + X group between five and seven years. The radical-only group is small, but tends to behave in a similar manner to the radical + X group.

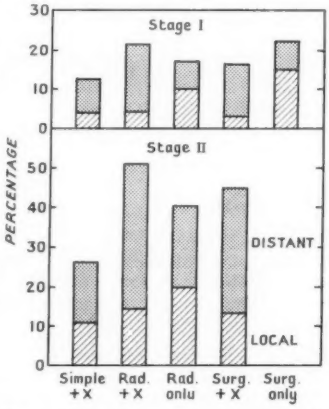


Fig. 7—Percentage of recurrences within two years according to whether they first occurred locally or at a distance. Surgery only in stage II is the same as radical only.

In fig. 7 the recurrences in the first two years are divided according to whether they occurred " locally " (i.e., within the treated area of breast and axilla) or at a distance. The incidence of local recurrence in the two groups of stage-II cases treated with surgery followed by irradiation is similar, and the greater recurrence-rate in the radical + X group is almost entirely accounted for by distant metastasis. The effect of X-radiation would appear to be to reduce the risk of local recurrence, as is evidenced by the higher proportion of local recurrences in the radical-only group. The figures for the stage-I cases show a similar trend although the differences in the incidence-rates for distant recurrences are not this time significant.

We have also extended our survey to include stage-II cases treated in 1951 and 1952 by either simple or radical mastectomy with postoperative irradiation. The two-year and five-year net recurrence-free rates in table II for the whole period 1947–52 show similar differences to those for the period of the main survey.

These results are consistent with the argument, either that tumour cells are more likely to be liberated and disseminated by the radical operation, or that radical surgery lowers the patient's general condition so that cells that have already disseminated form active foci for metastatic growth instead of lying dormant for some years. The latter explanation would account more reasonably for the fact that at seven years the recurrence-free rates in our groups are the same.

TABLE III—STAGE II NET RECURRENCE-FREE RATES 1947–52

Treatment	No. treated	Net recurrence-free rate at:		% of recurrences	
		2 yr.	5 yr.	Local	Distant
Simple + X	37	71·5	57·2	8·6	20·0
Radical + X	107	50·5	36·8	13·1	36·5
Difference		21·0 ± 9·0	20·4 ± 9·6		

Two possible factors must be mentioned which might account for the observed results without presupposing that in stage-II cases radical surgery is inferior to the simple operation. The first is the fact that in 17 of the 29 cases in the simple + X group, the preoperative clinical findings were in doubt, and the staging was decided by the presence of significant axillary glands when the patients were referred for irradiation. This could conceivably mean that a few preoperative stage-I cases were included. As against this possibility, we have found no observable difference between the survival-rates of these cases and the rates for the remainder of the group who were staged preoperatively.

The second factor is that we do not know what degree of selection may have been exercised by the surgeons themselves. We have already shown that they were reluctant to rely on simple mastectomy in stage-II cases; and it is, therefore, possible that the simple + X group contains a higher proportion of cases in which only one or two glands were palpable in the axilla. The effect on prognosis of the extent of axillary involvement has been well demonstrated by Berven (1949). Alternatively, surgeons may have reserved the radical operation for patients in better general condition, and the results may thus be biased against the simple mastectomy. There is no answer to this criticism of the comparability of our groups, and such a defect is almost certain to exist in any other retrospective survey.

Discussion

We have presented the figures given in the previous section, not because they prove conclusively that there is a difference between the results obtained by the two surgical procedures, but because they indicate the lines along which the problem of simple versus radical mastectomy should be investigated. Previous reports and our own experience indicate that a patient is not likely to do worse if she is denied radical mastectomy. Nevertheless the possibility of an increased recurrence-free period for a considerable proportion of stage-II cases when simple mastectomy and postoperative irradiation are used cannot be lightly dismissed. A proper clinical trial is the only way in which the problem can be resolved, and we have been most fortunate in obtaining the cooperation of surgeons in our area who have agreed to participate in such a trial. Its design is briefly as follows:

The aim is to compare the results of (*a*) radical mastectomy plus postoperative irradiation, and (*b*) simple mastectomy with limited axillary dissection plus postoperative irradiation in the treatment of stage-II carcinoma of the breast. The definition of stage II is that used in analysing the present series, and the surgeon to whom the patient is initially referred decides whether

the patient shall take part in the trial. Once the case is put in the trial, a card containing all relevant clinical information is completed and sent to the Radiotherapeutic Centre, Addenbrooke's Hospital. A random number is then allocated and, on the basis of this, the type of treatment is selected and communicated to the surgeon.

With the surgeons already participating, it is estimated that approximately 40 patients per year will enter the trial. In three years we should, therefore accumulate about 60 patients in each group. With these numbers we shall stand an 80% chance of detecting, at the 5% level of significance, a difference in two-year recurrence-free rates of the magnitude found in the present series (i.e., the answer on two-year rates should be known in five years). It is possible that other surgeons may also participate, in which case the numbers will be increased and the overall time reduced.

The fruitlessness of interdepartmental comparisons is now well recognised. We hope, therefore, that we shall be able to carry through this clinical trial successfully.

Summary

The results of treatment of 705 cases of carcinoma of the breast with a seven-year follow-up are described.

In stage-II cases the recurrence-free rates at two and five years were significantly higher with simple mastectomy than with radical mastectomy, but the possibility that this difference was due to selection cannot be excluded.

A clinical trial to compare radical with more conservative surgery in stage-II cases has been initiated.

We must first thank the surgeons, general practitioners, National Health Service executive council officers, and officials of Somerset House for their assistance in tracing the patients in this series. In particular we are most grateful to Mr. P. R. Ghey, Mr. V. Pennell, and Mr. B. M. Truscott for giving us details of their private cases. We must also record our appreciation of the work done by members of the nursing and records staff in tracing and sorting notes. We wish to thank Prof. J. S. Mitchell for his advice and encouragement throughout this investigation and in the preparation of this paper. Our thanks are also due to our colleagues in the Radiotherapeutic Centre for helpful comments and discussions. Finally we should like to record our appreciation of the enthusiastic way in which the surgeons and radiotherapists have agreed to participate in a clinical trial.

REFERENCES

Berkson, J. (1942) *in* Carcinoma and Malignant Lesions of the Stomach (edited by W. Walters, H. K. Gray, and J. T. Priestley); p. 467. Philadelphia and London.
Berven, E. (1949) *Amer. J. Roentgenol.* **62,** 320.
Bond, W. H. (1957) Annual Cancer Report, United Birmingham Hospitals; vol. 3, p. 5.
McWhirter, R. (1955) *Brit. J. Radiol.* **28,** 128.
Smithers, D. W., Rigby-Jones, P., Galton, D. A. G., Payne, P. M. (1952) *ibid.* suppl. 4.

NEW YEAR HONOURS

THE list of honours published on Jan. 1 contains the names of the following members of the medical profession:

Knights Bachelor

MILTON AUGUSTUS STRIEBY MARGAI, M.B.E., M.B. Durh.
Premier, Sierra Leone.

ARTHUR WILLIAM MORROW, D.S.O., E.D., M.B. Sydney, F.R.C.P., F.R.A.C.P.
Honorary physician, Royal Prince Alfred Hospital, Sydney.

ARTHUR PEREGRINE THOMSON, M.C., M.D. Birm., F.R.C.P.
Professor of therapeutics and dean of the medical school, University of Birmingham.

C.B. (Military)

Major-General ROLAND ANTHONY BENNETT, M.D. Edin., F.R.C.P.E., Q.H.P.

C.M.G.

NORMAN LACE CORKILL, M.D. Lpool.
Health adviser, Aden Protectorate.

C.B.E. (Military)

Surgeon Captain CHARLES BOYD NICHOLSON, M.B. Lond., R.N. retd.

Colonel ALISTAIR GORDON DONALD WHYTE, M.B.E., M.B. Aberd., F.R.C.S.E., late R.A.M.C.

C.B.E. (Civil)

MURIEL EMMA BELL, M.D. N.Z.
Nutritionist, New Zealand Department of Health, and supervisor, nutrition research department, Medical Research Council of New Zealand.

BRICE RICHARD CLARKE, M.C., M.D. Belf.
Consulting chest physician, Northern Ireland Tuberculosis Authority.

ARTHUR RICHARDS CULLEY, M.D. Wales
Principal medical officer, Welsh Board of Health.

IVAN DE BURGH DALY, M.D. Cantab. and Birm., F.R.C.P., F.R.S.
Lately director, Institute of Animal Physiology (Babraham, Cambridge), Agricultural Research Council.

MICHAEL GELFAND, O.B.E., M.D. Cape Town, F.R.C.P.
Physician, Salisbury Hospital, Southern Rhodesia.

JOHN ALEXANDER JAMES, O.B.E., M.B. Sydney, F.R.C.S.
Of Braddon, Australian Capital Territory; for services to the community.

GEORGE CARMICHAEL KELLY, M.D. Aberd., Q.H.P.
Senior administrative medical officer, South Western Regional Hospital Board.

ALAN BRUCE LILLEY, M.B. Sydney
Formerly chairman, Hospitals Commission, New South Wales; now medical director, Cancer Council, New South Wales.

EDWARD ERIC POCHIN, M.D. Cantab., F.R.C.P.
Director, department of clinical research (Medical Research Council), University College Hospital Medical School, London.

KENNETH ROBSON, M.D. Cantab., F.R.C.P.
Civil consultant in medicine, Royal Air Force; physician, St. George's Hospital and Brompton Hospital, London.

O.B.E. (Military)

Surgeon Commander ARTHUR FAWCETT MILLER BARRON, V.R.D., M.D. Edin., R.N.V.R. retd.

Lieut.-Colonel GEORGE LEE RITCHIE, M.B. Aberd., R.A.M.C.

O.B.E. (Civil)

GORDON ANDERSON, M.B. Edin.
Chairman, Birmingham No. 2 medical board.

MAURICE AILWYN BYER, M.B. Edin., M.P.H. Harvard.
Director of medical services, Barbados.

DAVID ALEXANDER CANNON, M.B. Glasg.
Senior specialist (pathologist), Federation of Nigeria.

CECIL JOHN CELLAN-JONES, T.D., M.D. Durh., F.R.C.S.E., D.L., J.P.
Chairman, Swansea Disablement Advisory Committee.

WILLIAM JOHN LYON DEAN, M.B. Aberd., J.P.
Lately provost of Lossiemouth.

PETER ROYLANCE DELAMOTHE, M.B. Sydney
Medical practitioner, Bowen, Queensland.

JOHN WILSON KYLE, M.B. Belf.
For services to rugby football in Northern Ireland.

IAN ALEXANDER MCGREGOR, L.R.C.P.E.
Director, Medical Research Council Laboratories, Fajara, Gambia.

PHILIP WHITESIDE MACLAGAN, M.C., M.D. Edin.
General practitioner and medical officer of health, Berwick-on-Tweed.

ISIDORE ROWLAND ROSIN, M.D. Dubl., F.R.C.S.E.
Medical practitioner, Salisbury, Southern Rhodesia.

JOHN ELVIN RUSBY, M.C., T.D., L.M.S.S.A., J.P.
General practitioner, Leeds.

CYRIL JOSEPH TONKIN, M.B. Melb.
Physician, Toorak, Victoria.

ANNIE DORIS WILSON, M.B. Edin.
Physician, Edinburgh Medical Missionary Society Hospital, Nazareth.

M.B.E. (Military)

Major HENRY HERBERT BUNCKENBURG, E.D. R.N.Z.A.M.C.(T.F.)

Major BRIAN DEVLIN, M.B. Lpool, R.A.M.C.

Major HERBERT SAMUEL GAVOURIN, M.B. Lond., M.R.C.O.G., R.A.M.C.

Captain JOHN FRANCIS HICKEY, L.R.C.P.I., R.A.M.C.

M.B.E. (Civil)

JOSEPH ANDREW ARRATTA, M.B. Sydney
Medical practitioner, Muttaburra, Queensland.

CLARENCE ERIC STANLEY BAILEY, M.B. Edin.
Medical superintendent, Holberton Hospital, Antigua, Leeward Islands.

JOAN CATHERINE CLATWORTHY, M.B. Lond.
For public services in the Western Region, Nigeria.

CHARLES GIBBONS SEYMOUR, M.R.C.S.
Member, National Service medical board, Southampton.

The Wider World

MALNUTRITION IN UGANDA

Examination of an Official Statement

JOHN MCFIE
M.A., M.D. Cantab.
LATELY MEDICAL OFFICER (NUTRITION), UGANDA MEDICAL SERVICE

" Wherever malnutrition exists, it is always the children who suffer most. Because medicine in the developing countries has given so little attention to the children the existence and the gravity of malnutrition has been overlooked for too long . . . For years we have known how to diagnose and prevent protein malnutrition, and how to cure all but the moribund patients. It is not scientific knowledge that is lacking: it is the will to organise the necessary services, and give adequate training to the necessary medical personnel."—Dr. CICELY WILLIAMS, Milroy lectures for 1958.[1]

To some these may have seemed vague generalisations, applicable perhaps to a few areas here and there in the tropics. In fact, these conditions are true of many of our Colonies where failure to take into account the state of public health, and ignorance of what has been achieved in other parts of the world, result in unrealistic medical policies. It is for this reason, and with these principles in mind, that I have taken the unusual step of looking at the problem of malnutrition in Uganda in terms of the speech on this subject made by the Under-Secretary of State for the Colonies in the last but one session of Parliament.[2]

Malnutrition and Child Mortality

Mr. John Profumo was replying to an adjournment speech by Mr. J. T. Stonehouse; and the first point concerned the size of the problem and its relation to child mortality. Data from the 1948 census showed that the mortality of children under the age of 14, for Uganda as a whole, was about 400 per 1000.[3] This figure was inferred from the age-distribution of the population, but it has been supported by figures collected in detailed village sample surveys, where child mortalities ranged from 170 to 570 per 1000,[4] and by surveys conducted in conjunction with the World Health Organisation in which local child mortalities ranged from 240 to 540 per 1000. From a neighbouring area of Tanganyika, the East African Medical Survey has reported a mortality under 5 years of 300 per 1000, of which 250 was infant mortality.[5] The Under-Secretary was at pains to emphasise the unreliability of vital statistics, and mentioned also the alleged inaccuracy of birth and death registration; but this is irrelevant as far as the quoted mortalities are concerned, since these were obtained by different methods and over a wide area. The consistency of the figures suggests in fact a fair degree of reliability; and even the Under-Secretary concluded by " not denying the general tendency, but it ought to be put in the right relationship ".

In her lectures Dr. Williams said that " in the absence of vital statistics, some information may be gathered from census figures, from sample areas, or from analogous conditions where statistics are available ", and that in many developing countries the mortality between the ages of 1 and 5 years was a more sensitive measure of the health of the community than the infant mortality. Wills and Waterlow [6] gave detailed evidence suggesting that mortality in the 1–4 age-group may be regarded as an index of malnutrition. In Uganda, comparable figures are not available, but the W.H.O. surveys showed the incidence of clinical signs of malnutrition, chiefly of kwashiorkor, to be highest in the 1–3 age-group, and that this incidence is significantly related to child mortality.[7] The proportion of children brought to rural dispensaries with frank signs of malnutrition varies with local conditions, but district averages range from 4% to 20%; the present estimate for the whole country is at least 25,000 cases annually. This indicates, however, only the numbers in whom malnutrition has reached clinical proportions: of those who attend Dr. H. F. Welbourn's clinics, growth records show that the *majority* fail to maintain the weight-gain of well-fed babies after their sixth month [8]; and the W.H.O. surveys showed that even in the moderately well-off families, children in the 1–5 age-group were getting only 50–60% of the recommended allowance of protein in their diet.

The Under-Secretary accepted malnutrition as a major cause of mortality among children, but in the same sentence sought also to implicate personal hygiene. If by this he meant washing, it is worth observing that regard for cleanliness is at least as high among most peoples in Uganda as it is in England: furthermore, unwashed children get scabies and conjunctivitis, but these are not commonly fatal. If he meant toilet habits, it is true that they are not up to the standard usually maintained in Britain, and many children have hookworms or roundworms; but the association of these even with morbidity is uncertain, as correspondence in *The Lancet* has suggested[9]; and in Uganda the surveys conducted with W.H.O. help showed no significant clinical differences between groups that were and were not harbouring hookworms or roundworms.[10] Finally, in the area in which " personal hygiene " in either sense is probably regarded most lightly, child mortality is lowest; but this is because it is mountainous and has little malaria.

Child-welfare Clinics

The 1948 census showed that over 17% of the population (now probably nearly 1 million children) were children under 6 years: nearly a third are children under 10 years. In 1955 a committee under the chairmanship of Prof. A. C. Frazer reviewed the functioning of the Uganda Medical Service [11]: its detailed recommendations were largely administrative, and it dealt with matters of health in generalities; but it stated that " away from the centre, child health services have lagged behind other branches of medical development in the Protectorate " and recommended that " a post should be created for a senior medical officer in the Medical Department primarily concerned with the development of an effective maternal and child health organisation throughout the Protectorate ". The Uganda Government replied that it was the intention to build " health centres " in appropriate places, at which child-welfare work would be encouraged, but the " Government does not consider that a new post of Senior Medical Officer, to deal exclusively with maternal and child health and welfare organisation, is required. It is felt that maternal and child-welfare work can be adequately covered by the Senior Medical Officer in charge of Health Education ".[12] In the debate on this reply in the Legislative Council, Prof. H. J. Croot, a member of the Frazer Committee, deplored this decision, observing that the new buildings would be monu-

1. Williams, C. D. *Lancet*, 1958, i, 863, 920.
2. *Hansard*, July 7, 1958, col. 158.
3. Martin, C. J. *Popul. Stud.* 1953, **7**, 181.
4. McFie, J. Nutrition Surveys. Entebbe, 1956.
5. East African Medical Survey. Annual Report. Nairobi, 1952.
6. Wills, V. G., Waterlow, J. G. *J. trop. Pediat.* 1958, **3**, 167.
7. Gongora, J., McFie, J. 3rd C.C.T.A. Inter-African Nutrition Conference, Luanda, Angola, 1956.
8. Welbourn, H. F. *J. trop. Pediat.* 1955, **1**, 28.
9. *Lancet*, 1958, i, 857; *ibid.* 1958, ii, 373.
10. Jacob, G. F., Norris, T. J. 3rd C.C.T.A. Nutrition Conference, 1956.
11. Report of Committee on Medical Services; paras. 7.3.3, 7.5.3. Entebbe, 1955.
12. Statement by the Protectorate Government; para. 44. Entebbe, 1956.

ments to the children who died because of an inadequate child-welfare programme. The subordination of maternal and child health services to the medical officer in charge of health education has nothing to recommend it, and the small advance made in the services in the past three years bears witness to this.

The Under-Secretary stated that there were eight child-welfare clinics, held in the three large towns. In fact, if the mission health services are taken into account, there are probably half a dozen more; but even this touches only a tiny proportion of all children. (The group of clinics round Kampala, which officially constitutes the Child-welfare Unit, has been built up over the past eight years by Dr. H. F. Welbourn, whose goodwill and patience have resulted in the collection of an unparalleled body of data on the health of African children, and have won the devotion of thousands of African mothers.)

"At the present time," stated Mr. Profumo, "it is only in the more sophisticated areas of the Protectorate that parents are willing to use child-welfare clinics as distinct from sick children's clinics, so the Government are paying greater attention to welfare work in sick clinics which are held in most hospitals and dispensaries." The essential feature of a child-welfare clinic, as opposed to a sick-children's clinic, is that the mother brings her child fairly regularly, whether or not he is ill; it may therefore be assumed that by "use" the Under-Secretary meant "attend regularly". Parents cannot use child-welfare clinics unless they exist: sick clinics, particularly in rural hospitals and dispensaries, have neither the equipment nor the atmosphere for child-welfare work. Moreover, this distinction between sophisticated and unsophisticated is invidious. Concern for the health of one's child is not exclusive to sophisticated peoples, and Dr. Welbourn's data show that a large proportion of mothers attending her clinics come from the least-educated strata of the population.[8] Again, even in the most unsophisticated areas, whenever the local medical officer or nursing sister has started a regular child-welfare clinic, it has flourished—until the doctor or nurse was transferred. The misfortune lies in the fact that such endeavours are left entirely to personal initiative, rather than being an essential feature at medical centres in every district. Finally, in other territories—for instance, the West Indies [13]—the unsophisticated are induced to attend regularly by the free issue of milk powder or some other supplement.

Protein Supplements

This year, said the Under-Secretary, "some 15 tons of dried milk has been received from UNICEF for distribution in the Protectorate", and 45 tons is intended for next year (this has since been increased to 70 tons). But it is important to realise just how far a ton of skim-milk powder can be distributed. The supplement currently recommended by UNICEF is 40 g. per child per day. At this rate 1 ton is enough for 70 children for a year, and 70 tons for 4900; yet the number of children in the "vulnerable" age-group is nearly 1 million. The explanation of this discrepancy is that "distribution" does not mean distribution to the children before they show signs of malnutrition, but distribution to hospitals for treatment. "It is not the function of the Medical Department to undertake the distribution of food to the general population" is the principle laid down by the Director; and widespread free distribution of milk powder to young children is dismissed, and resale of milk powder, to be purchased with local Government funds, has been prevented. The milk powder requested from UNICEF is intended for treatment, and even then it will not suffice for more than a fifth of the young children brought to mission and Government centres with frank malnutrition. The extent to which Uganda has lagged behind other territories in this respect is shown in the accompanying table.

13. *Lancet*, 1958, i, 1123.

MILK POWDER ALLOCATED BY UNICEF TO SELECTED TERRITORIES AND THEIR ESTIMATED POPULATIONS OF CHILDREN (DIGEST OF UNICEF-AIDED PROGRAMMES [1958] U.N.-ECOSOC, 1958)

No. of recipients not stated

Territory	No. of children	Milk powder (lb. per year)	lb. per child
Uganda	2·0 million	156,000	0·07
Kenya	2·5 million	770,000	0·31
Tanganyika	3·3 million	448,000	0·14
Jamaica	560,000	3·2 million	5·7
Grenada	43,000	308,000	7·0

No. of recipients stated

Territory	Recipients	Milk powder (lb. per year)	lb. per recipient
Singapore	16,600	330,000	20
Trinidad	36,000	780,000	22
Sarawak	33,000	1·25 million	38

While considering allocations for assistance by UNICEF and other United Nations specialised agencies, it must be realised that these allocations depend on requests being made by the countries concerned; and in answer to a question the Colonial Secretary said [14] that "direct contact is maintained between the Governments of territories concerned and the Area Office of the Fund at Entebbe (in Uganda)". Nevertheless, another answer in the House of Commons [15] makes it doubtful whether this advantage is fully realised. Asked what allocations had been made at the latest meeting of the UNICEF board for assistance to maternal and child-welfare services, the Colonial Secretary replied, "An allocation of £16,000 was made to the Government of Kenya, and £17,800 to the Government of Tanganyika, for maternal and child-welfare services. No allocation was made, and none requested, in respect of Uganda". Subsequently, an official in Uganda explained this omission on the grounds that "aid for Uganda had already been approved from the Fund". It was stated that Uganda had received £119,000 in aid from UNICEF; but analysis shows that £40,500 was for leprosy control, £30,500 for community development, £15,500 for the teaching of pædiatrics at Makerere College, and £32,500 for "maternal and child-welfare services, training, and health education".[16] In view of the Uganda Government's earlier statement on the relative importance of child welfare and health education, it will be realised that this order of priorities was, in fact, reversed, and child welfare came at the bottom of the list. When the cost of such equipment as sound film projectors and recording equipment is considered, this is a small sum to cover so wide a field, and it is surprising that no further allocation was requested for the coming year.

When he stated UNICEF's allocation of skim-milk powder, the Under-Secretary mentioned that the Church World Service of the U.S.A. is also making a gift of dried milk "to be distributed to undernourished children in Buganda". But this is not in fact its purpose; and the gift should not be confused with the allocation from UNICEF. Whereas the UNICEF milk powder is intended specifically for treatment, the C.W.S. gift is an experiment in prevention and health education in practical terms.

The gift is a relatively small amount, at the rate of approximately 70 tons per year. The distribution is through the Protestant and Catholic mission medical centres, the clinics of the Kampala Municipal Council, Dr. Welbourn's clinics, and the dispensaries of the Buganda (African) Ministry of Health (whose policy is not subordinate to the Protectorate [British] Government). The amount issued is ½ lb. per week per child between the ages of 6 months and 6 years; and it may be added that instructions are to mix the milk powder *dry* with the child's banana or other food. As the total amount is limited (largely by the cost of rail freight from the coast), the area of distribution has been restricted to one district; and one aim of the scheme is

14. *Hansard*, July 30, 1958, col. 146.
15. *ibid.* July 28, 1958, col. 83.
16. *Uganda Argus*, Sept. 10, 1958.

to find out what proportion of the child population can be reached using existing centres and channels of distribution. Meanwhile, there has been an immediate and gratifying response to the gift: the numbers attending child-welfare clinics have nearly quadrupled, and the majority of this increase is made up by re-attendances; and from one of the distributing agencies comes a letter: " I am starting to receive letters from individual women and from presidents of women's clubs saying how grateful they are and claiming it has already made a big difference to the health of their children. The sister in charge of the leper camp maintains it has already made a very noticeable difference in the development of the children ". The participants in the scheme hope that the Uganda Government will be pleased to share in this gratitude, and to extend it more widely; in short, to include the local scheme in a country-wide distribution based on an appropriate allocation from UNICEF; but so far the official response has not been encouraging.

" But the provision of supplementary foods," writes Dr. Williams, " is symptomatic, not ætiological treatment." Certainly Uganda cannot expect to receive free milk powder indefinitely, although it is essential that the initial distribution in an area should be free, or at least very cheap. Other countries, such as Nyasaland and the Belgian Congo, have found that a demand is thereby created for supplementary foods: it is then necessary only to ensure that the supply is maintained, and that the price is not out of reach of those who need the foods—otherwise the present situation created by the purchase of expensive baby foods [17] will be aggravated. It would be quite possible for Uganda to conclude a trade agreement with one of the dairy-farming Commonwealth countries. Imported milk powder, however, is not the only answer: fish flour and groundnut flour are both excellent sources of protein, and Uganda produces both fish and groundnuts. The Uganda Fish Marketing Corporation, originally started with a Colonial Development and Welfare grant, has been sold to a private firm [18] and with it has gone a fish-drying and powdering plant; but the adviser on nutrition to the Federal Government of Nigeria has described the production and tests of a fine highly nutritive groundnut flour,[19] made after the oil was expressed. The new equipment needed was not excessive: and UNICEF has shown itself willing—in Nigeria, for example —to supply processing plant, provided distribution of the product to young children is assured.

A protein concentrate would also be a basis for adequate school meals, and the value of these supplements has been widely demonstrated—in the West Indies,[13] for instance. In Uganda, to quote the Under-Secretary's reply, " No dried milk powder, groundnuts or fish flour are provided by Government as diet supplements for schools. Schools which provide meals purchase food that is available locally and—this is an important point—that is acceptable to tribal prejudices ". The failure to establish an adequate school-meals programme parallels the neglect of an adequate child-welfare service; and the reference to " tribal prejudices " is a red herring of the same order as " personal hygiene ". Food taboos have inspired a number of exegeses (cf. Trant [20]), but it is important to distinguish between religious avoidance, distaste (such as *some* people have for ants and grasshoppers), and ignorance. As far as school meals are concerned, the only prejudice of consequence, in a few areas, is against fish; but this is a combination of distaste and ignorance, and even in areas where the prejudice exists schoolchildren have eaten fish *when it was available*. Nevertheless, most of Uganda's annual catch of fish is sold to neighbouring countries, and internal distribution is sadly deficient.

Another foodstuff which would be a valuable addition to the diet, having a higher protein content than the starchy roots and bananas, is in danger of acquiring a prejudice on the grounds of distaste; and this is maize flour. It is produced on a commercial scale, and many schools and institutions, and even some homes, use it as porridge; but too often when the sack is opened it is found to be weevilly, or when the meal is cooked it is found to be sour. The Uganda Government has been considering for at least three years some form of legislation to ensure the purity of foods offered for sale, and it is to be hoped that action is not long delayed.

Malnutrition in Adults

The burden of malnutrition does not fall on children alone: apart from its possible relation to the high incidence of such conditions as cirrhosis and carcinoma of the liver, it leaves its mark in poor physique in the adult.[21] [22] When to this is added an inadequate calorie intake, the result is a big drop in efficiency—a point emphasised by Trowell.[23] This combination of circumstances applies to a large proportion of unskilled labourers, employed to do physical work, who come from their villages to work in industries and plantations. In many territories, such as the Congo, there are stringent regulations about labourers' diet, and particularly the amounts of meat or fish. In Uganda, the Under-Secretary stated, " the Uganda Employment Ordinance does not place a statutory obligation on employers to provide their employees with food. The employment rule empowers the Labour Commissioner to require employers to provide rations according to a specified minimum scale. These rules have been applied to all employers whose labour is recruited under contract and from a distance. They are not applied to employers whose employees are locally engaged and who return to their homes daily ".

It must be made clear that, on those terms, the rules apply to only 10% of employees: last year the total African labour force was computed as 223,000, while those recruited under contract numbered 22,000.[24] Even to this small proportion of labourers the rule is not properly applied, for most of them work on the sugar plantations, and the Hindu plantation owners have been excused, on the grounds of their own religious beliefs, from supplying meat or fish, but they give their employees coupons exchangeable for meat at shops outside the plantations. The Labour Department also admits that even the specified minimum of fresh vegetables is not given, and excuses the employers on the grounds that fresh vegetables were difficult to obtain. In conditions like this, no excuse should be accepted, and a few prosecutions would strengthen the rule; yet in 1954–57 there were 84 prosecutions of employers for failure to provide proper housing, 113 for failure to maintain sanitary conditions, and 16 for failure to provide medical facilities, but *none* for failure to provide statutory rations.

Mr. Profumo's words give the impression that there are only (*a*) those labourers who come from a distance, who are recruited under contract, and (*b*) those who are locally engaged, who do not come from a distance. In fact, there is a third category (*c*) who are locally engaged but who nevertheless come from a distance. The proportion of (*c*) is hard to estimate; but it can be stated that though 28% of the labour force comes from outside Uganda,[25] only 10% (which includes inhabitants of

17. Welbourn, H. F. *J. trop. Pediat.* 1958, **3**, 157.
18. *Uganda Argus*, Nov. 14, 1957.
19. Report of Federal Adviser on Nutrition. Lagos, 1956.
20. Trant, H. *Lancet*, 1954, ii, 703.
21. Orr, J. B., Gilks, J. L. *Spec. Rep. Ser. med. Res. Coun., Lond.* 1931, no. 155.
22. Hiernaux, J. *L'Anthropologie*, 1952, **56**, 494.
23. Trowell, H. C. *East Afr. med. J.* 1955, **32**, 153.
24. Labour Department Annual Report. Entebbe, 1957.
25. International Confederation of Free Trade Unions. Report of Mission to East and Central Africa, 1958.

Uganda) is recruited under contract. Most of those coming from outside therefore fall into category (*c*), and it is probable that the majority of the whole labour force is in this group. It may be argued that these employees return to their homes daily; but these homes are rented rooms or huts shared with other labourers: they are not their family homes, where the wife or mother prepares an adequate meal, including the wild leaves and fruits in the sauces, which contain a lot of vitamin A. The labourers come " home " to a shared dish of maize meal and beans and within a few months they begin to join the ranks of those with night-blindness and xerophthalmia in the eye-clinic at Mulago Hospital.[4] Present regulations do not oblige any employer of this class of labour (and this includes the Public Works Department) to provide them with food.

The most trenchant criticism of the present policy was in fact made by the Labour Department itself: " Too little attention seems to have been paid to the value of a really first-rate ration, and too many employers are deluding themselves when they think that a raw labourer will, in fact, feed himself on a proper diet, if he has to buy his own food. Experience in other parts of Africa has proved conclusively that there is much to be said for ' spoon-feeding ' raw labour, provided the spoon contains meat, meal, nuts, beans, vegetables, sugar, salt, tea and fresh fruit. Output is bound to remain low where this is not appreciated ".[26]

Who is Responsible ?

Finally, the Under-Secretary considered Mr. Stone-house's question: Who is responsible in Uganda for dealing with the problem of malnutrition ? His reply did not mention the Minister for Social Services in Uganda, within whose province at that time fell the Medical, Education, and Labour Departments, and the Nutrition Advisory Committee; and, in enumerating in detail all the departments and units in any way concerned, Mr. Profumo gave the impression that there was no central authority which would examine and act on the whole situation. A number of almost independent groups working in the same field create competing interests which view each other with suspicion rather than with a desire to cooperate. His reply also gave the names of research organisations, which have nothing to do with public-health policy. The investigations by departments of Makerere College, and by the Uganda Government and the East African High Commission, have contributed to our knowledge of what steps to take; and the work of the M.R.C. infantile malnutrition research group speaks for itself; but these bodies are in no way responsible for measures to prevent malnutrition. On the other hand, it would have been relevant to summarise, or at least to mention, the reports of the study of income and expenditure, of the W.H.O. nutrition survey team, and of the Food and Agriculture Organisation adviser on fish marketing, and to state what action was proposed on the basis of these reports.

I find it hard to accept unreservedly the Under-Secretary's assurance that there is no evidence of complacency either on his part or on the part of the authorities in Uganda: the note of complacency was sounded immediately after the war [27] and has been sustained ever since. It was not my purpose, however, to make a personal or political attack: my intention was to emphasise that a major problem exists, and to point out that relatively simple measures have already proved themselves in other tropical countries. The present policy not only has its immediate consequences in weakness, ill health, and death: it serves also as an unworthy example to those who will one day be responsible for the medical services of their own country.

26. Labour Department Annual Report; para. 109; Entebbe, 1954.
27. Review of Nutrition in Uganda. Entebbe, 1945.

Parliament

Mental Health Bill

THE text of the Mental Health Bill introduced in the House of Commons on Dec. 17 by the Minister of Health [1] was published this week. The Bill contains substantial changes on the lines recommended by the Royal Commission on the Law Relating to Mental Illness and Mental Deficiency.[2] Its main features include the following:

Single code.—There is to be a legal code to cover both mental illness and mental deficiency, instead of a separate code for each as at present.

No " designated " hospitals.—The present statutory limitation of treatment of " persons of unsound mind " in "designated " hospitals is removed; and hospital authorities will be able to arrange that any kind of hospital may receive any type of mental patient, whether on an informal basis or under detention.

Appeal tribunals.—Mental health review tribunals, including legal, medical, and other members, will, on a regional basis, consider applications from patients (and relatives) for release from hospital. The tribunals will have power to discharge patients.

Categories of patients.—The single term " mental disorder " is introduced to cover all forms of mental illness or disability. Provisions for compulsory detention recognise four groups of mentally disordered patients—mentally ill, severely subnormal, subnormal, and psychopathic.

Detention safeguards.—Compulsory powers of detention will be exercisable only where no other appropriate methods of dealing with a patient are available. Apart from criminal court cases no judicial order will be required. Two procedural safeguards introduced against improper detention are: (*a*) that two medical recommendations will be needed in all cases (except in emergencies, where one will be sufficient for the first 72 hours); and (*b*) that patients will be able to apply to a mental health review tribunal at any time within six months after admission.

Powers of discharge.—The general rule will be that the nearest relative of all patients admitted under the new procedures will hold the power of discharge (at present this does not apply in the case of mental defective patients). Powers of discharge are also given to the doctor responsible for the patient's treatment, in addition to the hospital managers as at present, and (in cases of guardianship or patients detained in private nursing-homes) to the local authority.

Psychopathic and subnormal patients.—Patients in these two groups may be compulsorily admitted under the age of 21, but over the age of 21 only after court conviction or transfer from prison (except that patients of any age may be detained for not more than 28 days' observation). But psychopathic and subnormal patients will not be liable to be detained beyond the age of 25 unless: (*a*) they were originally admitted through the courts or transferred from prisons or approved schools; (*b*) they are considered to be dangerous to themselves or others.

Power of courts.—Mentally disordered patients of any age convicted in the courts may be detained in hospital for treatment or received into guardianship, if the hospital or guardian is willing and if the court considers this the most suitable course.

Protection of public.—If a court of assize or quarter sessions considers it necessary for the protection of the public, it may order that a mentally disordered person convicted before it or (in the case of quarter sessions) committed from a magistrates' court, shall not be discharged without the Home Secretary's

1. See *Lancet*, 1958, ii, 1376.
2. See *ibid.* 1957, i, 1187.

consent. While such a restriction is in force, patients will not have access to a mental health review tribunal, but the Home Secretary will be able to refer to the tribunals for advice at any time.

Board of Control.—The Board of Control is wound up. Some of its functions will be carried out by the new review tribunals, others by the local authorities and the Minister of Health. The three State hospitals—Broadmoor, Rampton, and Moss Side—will come under the direct management of the Minister of Health. They will not be incorporated into the National Health Service administrative system.

The shift of emphasis from hospital to community care for mental patients which the Royal Commission recommended and the development of local-authority services to this end, does not depend on new powers conferred in the Bill. The Bill, however, makes it clear that all the services, including residential accommodation, may be provided by local health authorities under the National Health Service Act, and makes provision for the continuance of services which they at present provide under the Mental Deficiency Acts. Amendments are also proposed to the National Assistance and the Children Acts to allow authorities greater freedom to organise services for mentally disordered people within the framework of their general health, welfare, or child-care services under those Acts.

Public Health

Causes of Death

ACCORDING to a statistical report of the World Health Organisation,[1] the inhabitants of some of the economically advanced countries are almost as likely to die a violent death as to die in their beds: accidents, poisonings, violence, and suicide claim almost as many lives as all diseases taken together. In Canada, for example, in 1956, motor-vehicle accidents accounted for a death-rate of 22·1 per 100,000 population; all other accidents for a death-rate of 35·5; suicide for 7·6; and "homicide and operations of war" for 1·2. This adds up to an annual death-rate under the heading "accidents, poisonings, and violence" of 66·4 per 100,000 population, compared with a death-rate of 65·2 for all diseases except "ill-defined and unknown causes and senility", which account for a death-rate of 11·3.

This pattern of causes of deaths emerges when disease death-rates fall and when improved health statistics allow the "unknown and ill-defined" category to be reduced. Another factor is, of course, the increase in most countries in the number of deaths from accidents.

1. *Epidem. vit. Stat. Rep.* 1958, **11**, no. 10.

Infectious Diseases in England and Wales

Disease	Week ended December			
	6	12	20	27*
Diphtheria	4	2	4	3
Dysentery	1020	1208	1210	766
Encephalitis:				
Infective	2	7	6	3
Post-infectious	4	..	4	3
Food-poisoning	178	164	168	96
Measles, excluding rubella	8382	9447	10,117	8011
Meningococcal infection	28	19	19	17
Ophthalmia neonatorum	27	26	20	1
Paratyphoid fever	2	2	2	2
Pneumonia, primary or influenzal	496	520	527	409
Poliomyelitis:				
Paralytic	41	31	18	15
Non-paralytic	12	16	10	5
Puerperal pyrexia	206	187	179	100
Scarlet fever	1218	1294	1285	945
Smallpox	..	..	..	..
Tuberculosis:				
Respiratory	489	455	479	285
Meninges and C.N.S.	4	3	4	1
Other	46	52	58	35
Typhoid fever	1	2	5	2
Whooping-cough	749	641	532	286

* Not including late returns.

In England Now

A Running Commentary by Peripatetic Correspondents

"MEDICINE in the Tropics," said the senior M.O., "is not only different from what one sees in Europe, but borders at times on the incredible, if not the impossible." Before the year was over I had confirmed the truth of his words.

My new outpost had a small but well-equipped hospital. My Malay staff consisted of one sister and two male nurses. My predecessor had been removed with blackwater fever the week before, so I began without much of an introduction.

The first emergency did not take long to appear. A multiparous woman was admitted in extremis. Even her husband could not remember how many children she had had, but assured me proudly that it ran into double figures. To my horror I diagnosed a ruptured uterus. I had never operated on anything more serious than an appendicitis or inguinal hernia before, but the woman survived and I proudly kept her uterus in a jar—my first subtotal hysterectomy.

When she left, I patted her on the back and assured her that she need not fear to have any more babies. She was deeply grateful, though she did not appear to be convinced. Nine months later she came back, squatted by my chair and said, "I am pregnant again". "No," I said, "as it happens, my dear, that is impossible," while I was thinking of her uterus standing in the bottle on my shelf. But no matter what I said, she remained quietly insistent: and there was a definite bulge. "Must be a cyst," I thought, as I took an X ray—and there it was, a faint outline of a fœtal skeleton.

I packed her off to the base hospital with her fateful X ray, her uterus, and my resignation. In my letter I tried to explain. My resignation was not accepted, but later I returned to base hospital for a spell of training. The woman had returned in the meantime with her new baby son, named after me. My nights had been spent in an agonising reappraisal of the operation, as I wondered what in fact I had removed.

Not until my return and to the great hilarity of the whole staff, who made a point of discussing the technique of hysterectomy with me for years to come, was the mystery explained. The woman had had a double uterus and in my agitation I had not noticed the small other horn and had just removed the pregnant one.

It did one thing for me, though—I took up psychiatry.

* * *

No-one else would take on the job, so I had to be Father Christmas, being pulled into each ward by nurses screaming "Jingle Bells" at the tops of their voices. Only our 7-year-old osteomyelitis of skull claimed to have recognised me, only one child tried to hide behind his mother, and only two actually burst into tears on seeing me; so I thought I did quite well for a beginner. The mask, a papier-mâché contraption, which seemed to be afflicted with polycythæmia, gave me a bilateral temporal hemianopia, so that I had to be led about by Sister. Besides our patients, all the doctors' children came to get an addition to their own stockings, mixing cheerfully with the ward residents, including our query chickenpox, who had come out of his cubicle specially for the occasion. The whole thing passed off quite well, but I was livid to see the picture of my rival from the General Hospital in the local paper instead of my own.

* * *

We had been out at our occupational therapy (boatbuilding at L.C.C. evening classes) and were just about to slip over with the empties before closing time, our oldest trousers still covered in shavings, when a sonorous knock echoed through the house. A policeman some 7 ft. high carrying a miniature searchlight towered over our front door. Shivering somewhat, and searching hastily through our mind for any recent event that might have been misinterpreted, we aphonically asked his business. "Can you", he rumbled, "Tell me where Dr. Manglesprat lives?" It appeared that the noble constable had been scouring the district for this good doctor and at length had been referred by some neighbours to me. Although we could not

help him in his search, ever inquisitive we asked if we could be of assistance. After doubtfully looking us over once or twice, he said he supposed one doctor was very much like another and he hoped the inspector wouldn't chew him up but hop in. So we hopped, shavings and all, and were driven at great speed (using all the correct hand-signals) to a nearby constabulary where, it appeared, a gentleman had resented the imputation that he was drunk and disorderly. In the small fracas that followed someone had trodden on his foot. The minions of the law, ever mindful of their duty to the public, inebriate or otherwise, desired that this alleged injury should be diagnosed and treated with dispatch. "Proper sloshed he was", said the inspector cheerfully, not at all put out by my shavings and oil-stained sweater. "Take the doctor down to the cells."

It was our first experience of examining a patient whose sole motive was to mislead the doctor, with seven policemen watching what was more; but careful anatomical thought convinced us that an invisible injury to the left instep would find it hard to produce pain radiating down the left arm, so we had no hesitation in saying that he was fit to be detained and that no treatment was needed. We asked hesitantly if there was any money in this, and they said oh yes, we could have 30*s*. on the nail, or, if we wished, could put in a claim for something more. Ever hopeful we said we were a specialist (if only in boatbuilding) and claimed 3 guineas, which didn't seem to worry the inspector one iota. Life in the medical profession, all of a sudden, didn't seem to be too bad after all.

It was later that night they woke us up to say that our alcoholic friend had assaulted the dog-handler on being moved to another station and the dog had bitten him; would we come again and treat him please? Medical life seemed pretty miserable again, but it occurred to us that we had no anti-tetanus, and neither had they. And that was the end of the matter. Very much the end we fear, for we haven't been paid yet.

* * *

Alarmed by recent literature collating inertia with silting up of the vital vessels, my Christmas presents to the family included hula hoops. The children were "naturals" at it; my wife after a brief course was well on the way; I was a definite flop. The wretched thing just wouldn't go round. Behind locked surgery doors I contorted, distorted, dislocated; but it just fell with a dull thud on my toes. I wriggled and waggled, but it still fell lifeless. Assuming on each occasion I must have the wrong hoop I tried them all, but gravity appeared well distributed between them—they all consistently dropped dead.

Christmas Day was ruined. I needed more and more solid and fluid sustenance after each attempt, with the associated vision of a dissolving liver and floating fat globules ever before my eyes. The family became increasingly suspicious of my disappearances and my worsened physical state after them—I am really a most abstemious man. Activity became more and more restricted. I needed longer and longer pauses during which I visualised the sclerotic vessels narrowing. I became gloomier and gloomier. Finally, bruised, shocked, injured, and mentally cowed, with vessels silting up all round, in deepest depression I slumped over the desk and penitently began to compose "another case of multiple injuries".

* * *

From the doctor's postbag:

Dear Doctor,

I have had real good night sleep. Now would you kindly let my husband know. Have I to take 4 heart tablets and just same with along medicine I got. also do I have to take little tablets as well 4 a day and also have I to take green ones 2 at night. Or have I just to take 4 heart besides 3 times medicine a day and brown ones 4 times a day and 2 green ones at night and just let him know which as to be taken with medicine please and oblige.

P.S.—Please let me know what as to take. I av wedding on Saturday.

Mrs. MAGGIE BULLOCK.

Letters to the Editor

MEDICAL SERVICES REVIEW COMMITTEE

SIR,—In your issue of Dec. 6 you kindly published the names of the members of the Medical Services Review Committee which has been set up by the Royal Colleges and Scottish Royal Medical Corporations, the Society of Medical Officers of Health, the College of General Practitioners, and the British Medical Association, to review the provision of medical services to the public, and their organisation, in the light of ten years' experience of the N.H.S.

From conversations which I, and members of my committee, have had with other members of the profession, it appears that there may be some misunderstanding as to the purpose and scope of our inquiry, and I would like to take this opportunity of emphasising that we do not regard ourselves as having been appointed merely to carry out yet another investigation into the operation of the National Health Service.

Our terms of reference make it clear that we have to examine the medical services in this country in the light of experience of the N.H.S. Indeed it would be wrong to pretend that any worthwhile study of the work of the profession could ignore the impact made upon it by the N.H.S.

We consider, however, that our terms of reference are much wider and require us to review the practice of medicine in all its aspects, and in all fields, clinical, social, and preventive, both within and outside the N.H.S.

We shall try to find out what advantages, and what disadvantages, the changing pattern of medical practice has brought to the patient, the community, and the doctor, and we hope our inquiry will be fruitful in indicating the lines on which future development should be planned.

We recognise the magnitude of our task, and to complete it successfully we shall need the cooperation of the profession and the public. At an early date we shall, therefore, be inviting evidence from professional bodies, and from organisations representing various sections of the community, but we shall always be pleased to receive the views of any organised body or individual touching the subject of our inquiry.

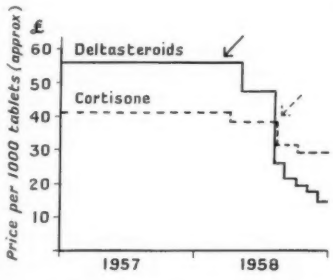
ARTHUR PORRITT
Chairman,
Medical Services Review Committee.

DANGERS OF "CHEAP" CORTISONE TABLETS

SIR,—The letter you published in your edition of Dec. 27 signed by Professor Rosenheim and Dr. Ross, of University College Hospital, provides us with an opportunity not only to rebut a most misleading letter, but to place before the medical profession in a timely way certain facts which are not only of public interest but which we believe will be of considerable concern to those who have some responsibility for effecting economies on behalf of the National Health Service and/or private patients.

We have little reason to doubt that it was this Company, which until recently had the London Teaching Hospitals Contract for the supply of standard deltasteroids and cortisone, which was the object of the attack in the letter referred to. This Company not only accepts this challenge but takes this opportunity through your columns, to acquaint the Profession with certain facts of which it may have been unaware.

In parenthesis, we note that Professor Rosenheim applies the word "cheap" to pharmaceutical products in a derogatory sense. This Company is, per contra, extremely proud of its record in providing the Profession with cheap pharmaceuticals. In support of this stand it is not uninteresting to recall that until this Company entered the field for the supply of these drugs in April, 1958 (deltasteroids) and August, 1958 (cortisone) prices had remained static as the accompanying graph will show.



Arrows indicate points at which Ward Casson Ltd. began to market "standard" corticosteroids.

We doubt very much whether any Company in this field will dispute either the figures embodied in this graph or the cause of the substantial price reductions demonstrated above, a cause in which this Company takes particular pride. In fact, our entry into this field brought down United Kingdom prices to a reasonable International level and this in turn resulted in considerable animosity towards this Company on the part of certain of our competitors. It is noteworthy that while we agree that our basic material has been imported—in this particular case from Switzerland, a country esteemed for the high quality of its pharmaceutical products—the Profession should know that we have been able to reduce these prices in spite of the considerable handicap of having to pay Key Industry Duty amounting to $33\frac{1}{3}\%$. This situation will maintain until our own manufacturing arrangements are in action, which will be shortly.

It never occurred to this Company that we should avoid being attacked, and in fact we have been continually slandered—sometimes from the most unexpected quarters—the attacks becoming almost hysterical once we had secured the London Teaching Hospitals Contract mentioned in Professor Rosenheim's letter. We took the precaution in anticipation of these attacks of having each batch of material independently assayed by an Analyst (Drug Testing) accredited to the Ministry of Health. The analyses show that the materials in question conform to the *B.P.* specification—both as regards the disintegration and composition.

This Company is therefore placing the whole of the facts of this case in the hands of unimpeachable authority in this field.

Reverting to the letter you have published, it is noteworthy that the potency of the cortisone-acetate tablets mentioned has not been challenged. The question of disintegration is however mentioned in Professor Rosenheim's letter, and we therefore wish to state that the independent analysis mentioned above makes it clear that the material in question was well within the tolerances of the *B.P.* specification. Indeed in the case of the analysis carried out by the Chief Pharmacist to U.C.H., the disintegration time amounted to $22\frac{1}{2}$ minutes—i.e., $7\frac{1}{2}$ minutes longer than the *B.P.* specification, an additional time which is considered wholly irrelevant. In support of this information we posed the following question to an eminent consultant. "What clinical difference would result from taking cortisone tablets with a prolonged, i.e., 25 to 30 minutes, disintegration rate, the tablets being in other respects perfect, i.e., cortisone content". The reply we have received indicates that even if the arbitrarily set disintegration time of 15 minutes were doubled there would be no reason to expect any decrease in efficacy—indeed to be pharmacologically inactive the disintegration time would have to be measured in hours. However irrelevant disintegration therefore is, it should be noted that the irregularity in the disintegration rate of cortisone-acetate tablets is a phenomenon known to analysts and manufacturers and has been a problem to more than one manufacturer.

It is therefore pertinent to ask whether this attack is really objective. Indeed one wonders whether all the facts in this case, other than the medical histories of the patients concerned, have been placed before Professor Rosenheim and his colleague.

To conclude what has inevitably been a rather long letter, we are of the opinion that the attack which you saw fit to publish emanated from a very subjective source and is a reprisal for this Company's efforts to introduce a spirit of healthy competition in the pharmaceutical industry. It is to be hoped that Professor Rosenheim and his colleague will look into the circumstances of this whole matter once again, will ensure that advice he has received of a pharmaceutical nature has been objective, and that he will take such action as is possible to rectify the damage which he has caused to this Company.

JULIAN SNOW
Director, Ward Casson Limited.

London, W.1.

SIR,—The London Teaching Hospitals Pharmacists' Joint Contracting Committee referred to in the letter from Professor Rosenheim and Dr. Ross negotiates contracts for the purchase of certain drugs on behalf of ten London undergraduate teaching hospitals. Contracts were placed for corticosteroid drugs which became effective on Aug. 1, 1958, after submitting tablets for examination to an independent analyst. Samples have been examined periodically since the contract came into force and the only departure from *B.P.* standards which has been reported is a lengthened disintegration time, the longest being 40 minutes. As soon as any batch has been shown to have a longer disintegration time than the official limit all hospital pharmacists in the contract scheme have been notified and the batch withdrawn.

The deterioration in the condition of the patients reported is most unfortunate and since the disintegration time of the tablets used was beyond the *B.P.* limits this must be considered as a probable factor in this deterioration, though it does not appear that all other possible factors have been eliminated before deciding on this one as the sole cause of trouble.

It is, however, regrettable that this was associated in the letter with cheapness and Continental origin since the committee believes that these factors are irrelevant to the main issue. It believes that there is not necessarily a close connection between "cheap" and "substandard" and that it is not true that trustworthy medicines can only be obtained by paying high prices. Indeed the committee had already taken advantage of a "break" clause in the contract and made a new one at a still cheaper price. The committee has consistently refused to purchase cheap drugs just because they were cheap, insisting always

that high standards of quality must be maintained and will continue to do so.

Suitable tests to find out whether the prolonged disintegration time could be related to the signs of adrenal insufficiency will be difficult to devise, but it is hoped that experiments in this direction will be carried out shortly.

Until this has been done we suggest that it would be unwise to attribute clinical failures to the quality of the tablets without further evidence.

Guy's Hospital, London, S.E.1. J. MOORE
Chairman.

G. RAINE
Secretary,
St. George's Hospital, London, S.W.1. London Teaching Hospitals Pharmacists' Joint Contracting Committee.

SIR,—The warning about "cheap" cortisone tablets, given by Professor Rosenheim and Dr. Ross is important, not only because of the danger to the patient but also because of the policy involved. In October a patient with Addison's disease, who was receiving daily 37·5 mg. cortisone supplied by her local chemist, was admitted for the investigation of amenorrhœa. Apart from this she was well, with a normal blood-pressure and serum-sodium level. During the first five days in hospital, while only simple investigations were carried out, she lost 5 lb. in weight and her serum-sodium fell to 130 mEq. per litre. Despite the dose of cortisone being increased to 50 mg. daily, she developed a hypo-adrenal crisis on the eighth day with a blood-pressure of 80/0 mm. Hg and a serum-sodium level of 118 mEq. per litre. With some difficulty she was resuscitated from this addisonian crisis, and the only cause found for her sudden deterioration was the quality of the cortisone tablets supplied in hospital. Like those at University College Hospital, they were manufactured in this country from material originating from the Continent. Not only was their disintegration time prolonged but their chemical composition is also in question.

Although the wish to economise on the cost of drugs is admirable, the hazards of purchasing possibly "substandard" material are considerable. In the past we have seldom had to concern ourselves with the purity of drugs, nor have we doubted that stringent tests of quality control have been carried out on each batch by the manufacturer. Our confidence must not be undermined by any false economy.

Westminster Hospital, London, S.W.1. R. I. S. BAYLISS.

SIR,—I was interested to see the letter from Professor Rosenheim and Dr. Ross in your issue of Dec. 27 on the subject of cortisone tablets which failed to disintegrate properly, as we have had a similar experience with thyroid tablets at this hospital. This seems to be another field for "eternal vigilance".

Northgate and District Hospital, Morpeth, Northumberland. C. GUY MILLMAN.

CLEANING OF GRIMY WOUNDS

SIR,—The letter from Mr. Wilkinson (Dec. 13) raises a rather neglected subject, and he rightly says that many of these skin contaminants are not easily cleaned off by the usual hospital solvents.

Working in factories manufacturing paints and varnishes of many types, which are made to adhere firmly, we have found that the best and safest method of cleansing the skin is for the patient to rub in petroleum jelly ('Vaseline'). This takes longer than a cleanser, such as 'Dirty Paws', which we have also tried, but is perfectly safe and unlikely to give rise to skin irritation. The petroleum-jelly emulsion with dirt is itself removed by soap and water.

Gerrard's Cross, Bucks. ROBERT PIPER.

NONCONFORMING NERVE-CELLS

SIR,—Dr. Menkes' interesting observations (Dec. 27) on neuronal nonconformism in the lateral geniculate body deserve some comment, both from the historical angle and in point of their interpretation. Firstly the matter of nerve-cell groups without apparent function—sensory, motor, regulatory, or "activating"—has a longer history than he mentions. Thus, Thomas Willis in 1684 wrote:

"When I did meditate and seriously discourse in my mind concerning the manufactory of the nervous Juyce, at last it seemed, by frequent Reasoning, that this is so. To wit, that the office of certain partes of the Brain & Cerebel is to procreate the Animal Spirits, and to dispense the same Juyce into the whole nervous stock. But, as I believe, there are other Partes which do not beget the Spirits: yet which being as it were lazie and indolent do use it for their own secret Economie. And to give force and substance to this Ratiocination, by Analogie we may every day discerne the like Behaviour amongst Men, whom we deeme not better than Parasites and Courtiers."[1] The same intuitive line was further elaborated by Hughlings Jackson[2] (1884), and, though Dr. Menkes refers to him, he has (I think) overlooked his most cogent reflections, which are so remarkably prescient as to deserve full quotation:

"Certain provisional divisions must be made", he wrote, "which I would remind the reader are admittedly arbitrary; they are not put forward as scientific distinctions. I suppose there to be a hierarchy of nervous centres according to the doctrine of evolution. . . . The doctrine simply affirms that there are to be differentiated in the nervous system many centres, which so to speak represent the whole organism, proceeding from the simplest to the most complex. Very briefly, we speak of the lowest centres, the middle and the highest centres, in ascending order of complexity, which become by ascent increasingly indirect in their representation and rerepresentation and at the same moment increasingly specialised. And lastly there is the final category of centres which I have named (following Spencer, but blaming him for none of my own crudities) 'supreme', in which the indirectness of representation is so compounded and refined that only specialisation remains, without other duty. I submit that at this supreme level, which is voluntary to the utmost and perfectly not automatic, the nervous arrangements reach the very apotheosis of evolution, with complexity in excelsis and, concomitantly, no degree of organisation to introduce 'involuntary' operation."

Now as to the theoretical implications of nonconforming nerve-cells, or, as I prefer to call them, "idler" neurones. It is current practice to liken the brain to electronic computer devices, and to look on it as a logical machine, which functions on a binary system of fire or not-fire of neurones in its activities of acquiring, storing, and using coded information. The comparison may not be pressed too far however, since the brain also shows, in amounts varying from one individual to another, a weak or strong tendency to illogicality and positive misinformation. This aspect of human cerebration has up to now proved puzzling to interpret in terms of cybernetics and communication theory. Dr. Menkes' work seems to offer the clue; for if there are indeed groups of idler neurones interspersed in

1. Willis, T. The Compleat Anatomy of the Brain. London, 1684.
2. Hughlings Jackson, J. Unexpurgated Writings (edited by J. Taylor). London, 1934.

cerebral circuits, they can provide the physical substrate for a system of improbability in the technical sense, an inbuilt information-losing process which has analogies with the process of entropy gain.

In simple terms it is the blueprint for a machina irratiocinatrix, that which (for better or worse) distinguishes man, not from the apes, but from the automaton.

Birmingham, 15. MICHAEL JEFFERSON.

URINARY CATECHOLAMINES IN THE DIAGNOSIS OF PHÆOCHROMOCYTOMA

SIR,—I do not dispute Dr. McMillan's criticism (Dec. 27) of the ethylenediamine reaction as a basis for the estimation of 5-hydroxytyramine in urine extracts; her elegant paper-chromatographic studies [1] go far towards proving her point.

I must, however, question her statement that " In the present state of knowledge then it would appear inadvisable to neglect the estimation of 5-hydroxytyramine in cases of suspected tumour ". Phæochromocytoma is a rare condition, and cases such as the one described by Litchfield and Peart [2] in which no excess of biologically active catecholamines could be demonstrated in the urine must be very rare indeed. Dr. McMillan does not mention this particular case (in which in fact there is no record of 5-hydroxytyramine estimation), but she hints at the possibility that in a case of this sort there might be a raised excretion of 5-hydroxytyramine. This hypothesis is of the greatest interest, but I feel that it does not justify the routine estimation of 5-hydroxytyramine in screening cases of suspected phæochromocytoma.

The London Hospital, E.1. J. T. WRIGHT.

TRANSPLANTATION OF FŒTAL TISSUE

SIR,—It was interesting to read the annotation of Dec. 13 describing the work of Professor Willis on transplantation of fœtal tissue, which referred to the possibilities of using cortisone and inbred animals for these investigations.

As part of a study on the heterotransplantation of human tumours and tissues, portions of human embryonic lung are being transplanted to mice and hamsters treated with cortisone acetate.

Pilot experiments have confirmed some of the observations of Toolan.[3] Histological examination showed survival of portions of lung grafts from a 14-week-old human embryo for periods of up to 91 days after transplantation to the cheek pouches of golden hamsters initially treated with cortisone acetate. The hamsters were from a closed colony, but not of an inbred strain. Examination of subcutaneous grafts in cortisone-treated C57 mice of lung fragments from fourteen human embryos between the 9th and 24th week of gestation showed histological survival of whole or part of the graft in about half the mice dying or killed 7 to 21 days after transplantation, and in about a quarter of the mice dying or killed 23 to 49 days after transplantation. In one case second and third passages of grafts were successful over a total period of 81 days. In addition to transplanting fragments from the more peripheral part of the lung, transverse sections of the main bronchi implanted as small rings will survive, and this technique may prove useful for investigating the action of carcinogens on bronchial epithelium. Adjacent portions of the embryonic lungs used were, in each case, grown in organ culture by Dr. L. M. Franks.

After transplantation there is a slight increase in the size of the graft, mainly due to a combination of proliferation of cartilage and dilatation of the bronchial branches. Some differentiation takes place in the grafts, but it is difficult to be certain whether the small spaces lined by flattened epithelium are true alveoli, resembling those described by Haemmerli [4] in heterologous transplants of rat-embryo lung to cortisone-acetate-treated hamsters, or whether they are a pathological cystic dilatation of bronchial branches similar to those described by Waddell [5] in subcutaneous transplants of mouse embryonic lung. Cyst formation also occurs in heterologous transplants of skin to DBA mice.[6] Pathological changes were seen in the grafts as stromal infiltration by chronic inflammatory cells. Nodules of lymphoid tissue were sometimes present in the stroma, and there were areas of bronchiolitis.

Several factors must be considered when relating histological changes seen in grafts to the normal intrauterine development of human embryonic lung. Thus the embryos themselves may be abnormal; traumatic and mechanical factors in separating lung from its original environment may affect growth and differentiation; and cortisone acetate, which is used to depress the host's resistance, may have an effect on the graft. Infection occurs more easily in animals treated with cortisone acetate.

Inbred C57 mice are easily obtained; but the hamster may be a more suitable animal for propagating human embryonic tissues, particularly when inbred strains become more readily available. The difficulty in obtaining suitable human embryonic tissue still remains.

A more detailed report of this work is in preparation.

Imperial Cancer Research Fund,
Central Laboratories,
London, N.W.7. FREDERICK C. CHESTERMAN.

IS INSULIN-COMA THERAPY OBSOLETE?

SIR,—Dr. Sargant's letter of Dec. 27 is of great importance. Many new substances and some techniques of value have become available since the 1954 edition of the physical-treatment textbook of which he is joint author. His attempt to assess the present value of insulin-coma therapy (I.C.T.) as compared with other methods is timely, because it is becoming possible to argue strongly that I.C.T. should now be considered obsolete.

Since 1954 new phenothiazine tranquillisers have been added to chlorpromazine, some more potent, and most of those in use in Britain probably less toxic. Even used alone, where dosage has been adequate, promazine (' Sparine '), acepromazine (' Notensil '), and perphenazine (' Fentazin ') have often given much symptomatic improvement in schizophrenics and other psychotics, and improvement after a course has often been sustained for months or over a year. Properly used, I believe, the phenothiazine drugs compare very favourably with I.C.T. Also, I.C.T. is of no value except in recent acute schizophrenia, whereas these tranquillisers can greatly improve the condition of chronic schizophrenics and sufferers from a variety of other reactions.

The most significant thing, I think, in Dr. Sargant's letter is his comment that his own group of schizophrenics who were treated by a combination of chlorpromazine and E.C.T. " did much better than was expected ". I have also found such a combination very effective; but I believe that the best results are achieved when the question of which *kind* of E.C.T. should be used, and in what pattern of dosage, has been fully assessed by the therapist.

The " ectonus " technique of E.C.T. devised by Dr. R. J. Russell and made available in 1956 is a method of continuous

1. McMillan, M. *Lancet*, 1957, i, 715.
2. Litchfield, J. W., Peart, W. S. *ibid.* 1956, ii, 1283.
3. Toolan, H. W. *Proc. Soc. exp. Biol. Med.* 1954, **86**, 607.
4. Haemmerli, G. W. *Trans. Bull.* 1958, **5**, 390.
5. Waddell, W. R. *Arch. Path.* 1949, **47**, 242.
6. Greene, H. S. N. *Cancer Res.* 1955, **15**, 170.

application of current of varying voltage for a period of 30 to 60 seconds. A control knob allows the therapist to alter the voltage so that clonic movements can be reduced to a slight twitching which indicates the course of the convulsion. Ectonus is a refined method which is both safer and more effective therapeutically than the traditional ("straight" or "one-shot") E.C.T. In 1953 Dr. Russell and his colleagues [1] described "itensified E.C.T." to which method later the term "fused-dosage" or "interrupted fused-dosage" (I.F.D.) was applied. Many of us who used it regarded this method as itself an improvement on the traditional method, but the same therapists would probably now regard I.F.D. as having been for the most part replaced by ectonus; but in acute mania, and some emergencies such as threatened suicide or refusal of food, one might prefer I.F.D. to ectonus for its greater potency and quicker results. No-one, I believe, with good experience of the two newer techniques and who had used them in the recommended way, would ever want to return to the cruder older method. But more than most, psychiatrists are slow to change.

Just over a year ago a series of articles was published giving a full account of the combination of ectonus E.C.T. with promazine drugs, the name ectonus-promazine therapy or E.P.T. being given to this planned combination.[2]

It is strongly recommended that, whether ectonus or other technique is used, the electrical part of the combined treatment should be given intensively—i.e., on successive days. With ectonus the course on average would be one dose a day for seven successive days. This corresponds closely to what Jacoby [3] calls "regressive shock therapy," [4] a method whereby E.C.T. is given by intensive daily dosage to the extent of producing a transient but severe confusional state. Dr. Jacoby's technique, however, involved the use of the older method of E.C.T. With E.P.T. good and lasting recoveries are achieved,[5] and the period of confusion lasts only four or five days and is much less severe than that described by Dr. Jacoby. It is important to note too that recovery of memory is rapid and complete.

Lennox Castle Hospital,
Lennoxtown,
Stirlingshire.

ALLAN A. MACDOUGALL.

STAPHYLOCOCCAL INFECTION IN HOSPITALS

SIR,—Your recent editorials on problems of infection in hospitals have been most praiseworthy. They have perhaps been just a little above the head of one who is so little advanced that he is still at the stage of having to battle with problems of ordinary domestic cleanliness;

but nevertheless your remarks not only are appreciated but also act as a stimulus to further efforts.

In an effort to get the walls of a hospital cleaned, I have been reduced to the somewhat dubious pastime of writing on the walls of the main corridors. Being a progressive individual, I felt that I could combine in one action both a cleansing and an educational effect upon our administrators by writing in water on a background of dirt the words shown in the accompanying photograph.

To illustrate further my difficulties I may add that my initial efforts were not successful. The words were merely smeared out, and the smears remained for ten days. It was only when I was observed by a member of the hospital administration actually having photographs taken that something was done about it.

You can easily imagine that at one stage in my campaign I felt that I might have to emulate that eccentric character of the time of the Great Plague, Solomon Eccles, and face the management committee dressed in a loin-cloth and wearing on my head a brazier of live coals shouting the words "After the Pestilence cometh the Fire. Prepare to meet thy Doom". I would be quite prepared to do this if I thought it would do any good—which I doubt—but I feel sure that the support of your editorials and valuable space will prove far more effective.

Meanwhile, just in case, my wife and daughter have started to knit me a loin-cloth.

Gateshead,
Co. Durham.

STANLEY WAY.

"REGISTRAR PROBLEM"

SIR,—Have those who could act on the registrar problem never read *Twenty Years A-growing* by Maurice O'Sullivan? In which the following truth is written: "Did you never hear how the life of man is divided? Twenty years a-growing, twenty years in blossom, twenty years a-stooping and twenty years declining."

"NEARLY OUT OF BLOOM."

TREATMENT OF LEPTOSPIROSIS WITH OXYTETRACYCLINE

SIR,—We were interested to read the article on leptospirosis by Dr. Russell (Nov. 29).

Factors governing the fall in the mortality of leptospirosis include (*a*) better diagnosis identifying mild cases previously unrecognised, and (*b*) early diagnosis facilitating skilled medical and nursing care. Also of much significance in the improved prognosis of severe leptospirosis is the skilled application of modern knowledge in the early recognition of water and salt depletion and its remedy, and the maintenance of correct hydration and electrolyte balance. No longer is it true to say, as one writer did less than a decade ago, that more lives are lost by intravenous fluid administration than are saved by it.

Our decision not to have actual controls in our work [1] was deliberately taken. Much of the work on the diagnosis, clinical manifestations, and methods of treatment reported from post-war Malaya was done on security forces in British military hospitals.[2–6] The annual reports of the successive consultant physicians FARELF were a mine of information. Furthermore, we believed that there was sufficient evidence that penicillin was effective in man, provided it was given early enough, often enough, and in adequate dosage.[7–9] Accordingly, as so much work had been done in the previous five years on security forces in Malaya, from the same leptospiral environments that we were to draw our cases, we felt that the patients studied by our predecessors could act as phantom controls. Indeed, in the original script on our work, reference was made to these controls; but inadvertently it was not included in the work as published.

1. Russell, R. J., Page, L. G. M., Jillett, R. L. *Lancet*, 1953, ii, 1177.
2. MacDougall, A. A., Campbell, D. *Nursing Mirror*, 1957, **106**, Nov. 29, Dec. 6, 13.
3. Jacoby, M. G. *Brit. med. J.* 1958. i, 282.
4. Jacoby, M. G., Babikian, H. M. *N.Y. St. J. Med.* 1958, **58**, 2965.
5. MacDougall, A. A. *Brit. med. J.* 1958, i, 1180.

1. Mackay-Dick, J., Robinson, J. F. *J. R. Army med. Cps*, 1957, **103**, 186.
2. Hobson, A. C. M.D. Thesis, University of London, 1952.
3. Hughes, W. D. Annual Report of Consultant Physician, FARELF, 1954.
4. Fairburn, A. C., Semple, S. J. G. *Lancet*, 1956, i, 13.
5. Trimble, A. P. Annual Report of Consultant Physician, FARELF, 1955; *Proc. R. Soc. Med.* 1957, **50**, 125.
6. McCrumb, F. R. *Amer. J. trop. Med. Hyg.* 1957, **6**, 238.
7. Smith, J. *Brit. J. industr. Med.* 1949, **6**, 213.
8. Varfolomeeva, A. A. *Soviet Med., Moscow* 1951, **11**, 29.
9. Doherty R. L. *Aust. Ann. Med.* 1955, **4**, 53.

The results of treatment of our first dozen cases of leptospirosis with penicillin were so dramatic and so convincing that our conscience would not allow us to deprive our jungle fighters of penicillin. Our published results of 84 consecutive laboratory-proved cases of leptospirosis [1] should convince the most sceptical not only that penicillin is specific in the early days of leptospiral infection in man in Malaya but that the appearance of the Jarisch-Herxheimer reaction is also diagnostic. By the time one of us (J. M.-D.) had left Malaya in March, 1958, the total number of consecutive laboratory-confirmed cases of leptospirosis totalled 140. There were no deaths, and the response to treatment was as we have already outlined.

One of us (J. M.-D.) had seen cases of leptospirosis at Kinrara in 1955 treated with intravenous tetracyclines. Brisk and alarming febrile reactions followed in a matter of hours in so many cases that the intravenous therapy was abandoned speedily. Were these merely Jarisch-Herxheimer reactions similar to those which followed the administration of penicillin in our early treated cases, the true significance of which was lost on us at that time?

Our views on the treatment of leptospirosis are that early cases (in the first few days) can be cured with antibiotics, the rationale being that during this stage of septicæmia the organisms are still predominantly in the blood-stream. On destroying the leptospiræ, toxin is liberated, resulting in the Jarisch-Herxheimer reaction and the associated aggravation of the manifestations of leptospirosis. There is, however, at this stage insufficient concentration of toxin in the tissues, especially the myocardium, liver, and kidneys, to produce severe irreversible damage. After the first week the leptospiræ will be destroyed by the patient's own antibodies, but the concentration of toxins in the tissues will be greater then, because of the greater number of leptospiræ, and so greater damage results in these tissues. By the time this has happened, neither antibiotics nor antitoxins can be expected to be of particular value.

Returning to the early cases, it seems rational to combine antibiotics with leptospiral antitoxin to lessen or abolish the Jarisch-Herxheimer reaction. So far this has not been reported. The antitoxin would have to be polyvalent, remembering that many specific strains of leptospiræ are involved.

Dr. Russell implies that the answer to leptospirosis will not be known until an antibiotic is discovered which is effective against leptospiral toxins. Surely by definition an antibiotic is effective against organisms and not against toxins.

We would not subscribe to the view that leptospirosis in Malaya is always a mild disease. There were 3 fatal cases in Hobson's series of 27. Deep jaundice, hæmorrhage, anuria, and vomiting do occur. It is not always possible to decide which cases that appear mild at first will become gravely ill if specific treatment is withheld. There are also, of course, the occasional fulminating cases; but these are exceptional.

Dr. Russell also states that efforts must be made to raise the blood-pressure if it falls to dangerously low levels. We believe the contrary, since on occasion toxic myocarditis plays a significant part in the production and/or aggravation of hypotension. During the period of hypotension great care must be taken over the administration of fluids intravenously for fear of precipitating cardiac failure. In such circumstances we found that to raise the foot of the bed was an added danger to the life of the patient.

A patient with leptospirosis and epistaxis was treated with adrenaline nasal packs and soon after their insertion he went rapidly downhill and died a cardiac death. There was also a case of leptospirosis provisionally diagnosed as bronchitis with severe bronchospasm. He was treated by his regimental medical officer with penicillin, resulting in a Jarisch-Herxheimer reaction, and ephedrine which may or may not have precipitated the auricular fibrillation, confirmed by E.C.G. On admission to hospital penicillin was continued with excellent results. Ephedrine was stopped and in a matter of hours the E.C.G. reverted to normal.

In our view the best treatment to date of leptospirosis in man in Malaya, and the one which causes least discomfort to the patient, is undoubtedly adequate and repeated penicillin, begun in the first few days of the illness, combined with skilled fluid and electrolyte balance—and masterly inactivity.

Connaught Hospital (Army Chest Centre), Hindhead, Surrey. JOHN MACKAY-DICK.
Cardiac Department, The London Hospital, E.1. JOHN F. ROBINSON.

ANÆMIA IN PREGNANCY

SIR,—You stated in a leading article of Dec. 27 that the case for administering iron to pregnant women now seems proved. As evidence for this, surveys are quoted which claim to show that during pregnancy the incidence of anæmia increases. In fact these studies merely show that the incidence of hæmoglobin levels below those of "normal" healthy non-pregnant women is increased; to equate this with an increase in anæmia is to disregard the facts of pregnancy physiology. The problem of anæmia in relation to pregnancy is complex and the extensive literature has been recently reviewed.[1] The main facts are these.

The basic misconception seems to be that the increasing red-cell mass in pregnancy should keep pace with increasing plasma volume and thus maintain a constant hæmoglobin concentration. But these two fractions of the blood perform quite separate functions and are controlled by quite separate mechanisms. The increased plasma is required not only to carry the extra red cells but also to fill, for example, the greatly dilated skin vessels of the extremities for the purpose of dissipating fœtal heat. The red-cell mass increased only in response to a demand for increased oxygen transport and the mean increase of about 17% with an enhanced velocity of blood-flow more than covers the increased need for oxygen carriage. This favourable balance is confirmed by a *decrease* in the mother's arteriovenous oxygen difference during pregnancy.

It has been argued that the reduced hæmoglobin concentration must represent iron deficiency since it can be raised by giving iron. But iron is a specific stimulus to blood formation and it is well-known that the hæmoglobin concentration can be raised in any normal person by giving iron.

No advantage has been shown to result from raising of hæmoglobin levels in normal pregnancy and there may be dangers. The falling concentration of red cells results in a reduced blood viscosity which lessens the work of the heart and contributes to the maintenance of normal blood-pressure as the cardiac output rises.

The very wide individual variation in the extent of hæmodilution makes it impossible to give an arbitrary lower value for hæmoglobin concentration in normal pregnancy.

If a healthy woman in late pregnancy who has "never felt better" and who is not breathless on exertion has a hæmoglobin concentration of 60% then it is surely wrong to label her "anæmic" on the basis of a laboratory measurement which has no absolute meaning in pregnancy; until a more meaningful laboratory test is

1. Hytten, F. E., Duncan, D. L. *Nutr. Abst. Rev.* 1956, **26**, 855.

available the management must remain a matter for clinical judgment.

The B.M.A.'s subcommittee on nutrition is quoted as recommending a "minimum" iron intake of 15 mg. daily. The subcommittee in fact adopted the American N.R.C.[2] recommended allowance which includes a large factor of safety. Such an allowance may be a desirable social target for a population; it is not a physiological requirement for an individual. There is no evidence that the average diet taken by pregnant women in Britain is inadequate in respect of iron.

Midwifery Department,
University of Aberdeen.

DUGALD BAIRD
F. E. HYTTEN.

SIR,—In their interesting paper of Dec. 27, Dr. Giles and Dr. Shuttleworth have produced definite evidence that the incidence of megaloblastic anæmia is considerably higher than was believed. They quote the case-incidence of 1 in every 190 hospital confinements, from our paper published in 1957,[3] as being the highest reported previously, and suggest that intensive efforts at diagnosis would produce a case-incidence similar to their own (1 in 39).

We suspected that the diagnosis had been missed in a number of cases, and we stated [3] that the case-incidence was probably higher than 1 in 190 hospital confinements. In view of this, an attempt was made to determine the true incidence of the disease by careful hæmatological investigation of all women in the last trimester of pregnancy or in the puerperium with a hæmoglobin below 65%. The results of this investigation [4] revealed a case-incidence of 1 in every 67 hospital confinements for the period between January, 1956, and February, 1957. It is unlikely that the diagnosis was missed often during the period of this survey, and these figures should reflect the true incidence of the disease in the area served by Whiston Hospital (St. Helens, Widnes, Huyton, and Prescot). The difference between the case-incidence in our first and second surveys suggests, therefore, that the diagnosis is likely to be missed in 2 out of every 3 cases if intensive efforts at diagnosis are not made.

I should also like to comment briefly on the following points:

(1) *Seasonal incidence.*—The monthly case-incidence found by Dr. Giles and Dr. Shuttleworth does not suggest a seasonal prevalence. The seasonal incidence in my cases,[5] however, does support the findings of Gatenby [6] and Thompson[7] that the anæmia begins much more frequently in the late winter and spring. Clearly a definite conclusion cannot be reached until a review has been made on a series of cases collected over several years, during which period there have not been an appreciable number of undiagnosed cases.

(2) *Response to vitamin B_{12}.*—Folic acid almost invariably produces a good response and is therefore the correct treatment. The variable response to vitamin B_{12}, however, is of interest and requires further study. Previous reports suggest that vitamin B_{12} is usually ineffective when the total dose does not exceed 120 μg., but that larger doses frequently produce an adequate response. We obtained a good response in 12 out of 15 patients treated with vitamin B_{12} in divided doses up to a total of 700–3000 μg. It is surprising, therefore, that Dr. Giles and Dr. Shuttleworth found no response in all 4 cases treated by apparently large doses of intramuscular vitamin B_{12}, although the actual dose is not mentioned. It is probable, of course, that there are several ætiological factors which may vary from case to case, but it is unlikely that there could be a fundamental difference between the ætiology of the cases in Stoke and those in Lancashire. The criticism that some of our patients may have had pernicious anæmia is answered by either the presence of free acid in the stomach, the absence of a relapse, or a normal serum-vitamin-B_{12} level.

(3) *Parity.*—All the patients in our first series were multiparous. Intensive efforts at diagnosis, however, reveal that the condition occurs not infrequently in primigravidæ; 20% of Dr. Giles and Dr. Shuttleworth's patients were primigravidæ and 30% of the patients in our second series were primigravidæ, none of whom had a hæmoglobin level below 45%. It would appear from these findings, therefore, that the diagnosis is most likely to be missed in the first pregnancy.

(4) *Gastric acidity.*—The incidence of achlorhydria is approximately between 30% and 40%. I found that the degree of anæmia tended to be more severe in the patients with achlorhydria and postulated that the achlorhydria was a result of the severe anæmia.[4] Since then I have had the opportunity to repeat the gastric analysis ('Diagnex' method) two or three years later in 5 patients, in 2 of whom there has been a return of secretion of free acid. No conclusion can be drawn from these few results, but when they are taken in conjunction with the findings of Dr. Giles and Dr. Shuttleworth it seems probable that there is a return of secretion of free acid in about 40% of the patients with achlorhydria.

(5) *Blood-group distribution.*—Unlike pernicious anæmia, in which there is a significant increase in the incidence of blood-group A,[8] the blood-group distribution in our patients with megaloblastic anæmia of pregnancy and the puerperium (total 51 cases) was normal. The most significant abnormalities of blood-group distribution occur in diseases involving the alimentary tract, and the normal distribution in our patients is in keeping with the view that megaloblastic anæmia of pregnancy and the puerperium is not secondary to a disorder of the gastrointestinal tract. Before reaching a definite conclusion, however, the blood-group distribution in a larger group of cases should be assessed, and I would be most interested if Dr. Giles and Dr. Shuttleworth would calculate the distribution in their cases.

Liverpool. JOHN FORSHAW.

PLASMA-CALCIUM IN PRIMARY HYPERPARATHYROIDISM

SIR,—Dr. Ross's letter in your issue of Dec. 27 raises the question of whether or not a given body fluid may be regarded as a simple U/F of the plasma of the same individual. Certainly one cannot assume that this is so without supporting evidence, and in the case of cerebrospinal fluid there is some evidence that it is not so. Thus C.S.F. and plasma have quite different patterns of free aminoacids,[9] while the generally accepted values of C.S.F. calcium of about 5·0 mg. per 100 ml. (see, for example, Stutzman and Amatuzio [10]) are distinctly lower than the values usually obtained for ultrafilterable plasma calcium.

Another body fluid which I have investigated with Dr. A. C. Kerr is parotid-gland secretion. Again the aminoacid content was quite different in total amount and pattern,[11] suggesting that this fluid was not a simple ultrafiltrate of plasma. We also observed, in unpublished work, that the parotid-secretion calcium varied from 3·2 mg. per 100 ml. at a flow-rate of 0·5 ml. per minute to about 5·5 mg. per 100 ml. at a flow-rate of 2·4 ml. per minute. Even more disturbing was the finding that the

2. National Research Council Food and Nutrition Board Recommended Dietary Allowances. *Publ. Nat. Res. Coun. Wash.* 1953, no. 302.
3. Forshaw, J. W. B., Jones, A. T., Chisholm, W. N., McGinley, W. K. *J. Obstet. Gynæc. Brit. Emp.* 1957, **64**, 255.
4. Forshaw, J. W. B. *Postgrad. med. J.* 1958, **34**, 222.
5. Forshaw, J. W. B. *Lancet*, 1957, i, 1249.
6. Gatenby, P. B. B. *Proc. Nutr. Soc.* 1956, **15**, 115.
7. Thompson, R. B. *Lancet*, 1957, i, 1171.
8. *Brit. med. J.* 1956, ii, 723.
9. Dent, C. E. Lectures on the Scientific Basis of Medicine; chapter 12. London, 1952.
10. Stutzman, F. L., Amatuzio, D. S. *Arch. Biochem.* 1952, **39**, 271.
11. Rose, G. A., Kerr, A. C. *Quart. J. exp. Physiol.* 1958, **43**, 160.

maximal level of parotid-secretion calcium was not equal on the two sides of the body. We must reluctantly conclude that plasma ultrafilterable calcium cannot be correlated with either C.S.F. or parotid-gland-secretion calcium.

University College Hospital Medical School, London, W.C.1. G. ALAN ROSE.

PROSTATECTOMY

SIR,—I studied with great interest the excellent article by Mr. Ellis and Dr. Leatherdale (Dec. 6) on an anæsthetic technique for prostatectomy, especially in the poor-risk patient.

In Bristol, urologists perform a cystoscopic examination before deciding whether to continue with a transurethral resection or a retropubic prostatectomy. I do not know how common this routine is in other areas, but where it is the rule the technique of low-spinal and abdominal-field block does not offer the most desirable conditions for either the patient or the surgeon.

If it is decided to continue with a transurethral resection, the low-spinal block does not adequately cover all the operative stimuli and the field block is, of course, unnecessary. The answer seems to lie in a choice between spinal, epidural, or caudal analgesia.

With spinal analgesia, there will always remain a low irreducible minimum of chance neurological sequelæ, naturally diminished by experience and skill. But chance is still a factor of a talking if not of a walking advertisement which speaks against the technique.

Successful caudal analgesia gives safe and excellent operating conditions, but anatomical difficulties may prevent its use, and, of course, there is no certain test of having entered the caudal canal as there is with spinal or epidural analgesia.

Purposely induced hypotension is not only unsafe but unnecessary in these poor-risk cases. The surgeon requires an area of operation which is completely relaxed, whether for the resectoscope or the bladder and abdominal-wall retractors, and in which the vessels do not bleed too much. These conditions are seldom achieved by the general-anæsthesia-with-relaxant technique. If controlled ventilation is performed a greater strain may be thrown on the heart and circulation, diminishing cardiac output by interference with the normal venous return, and increasing oozing from the vessels of the prostatic cavity. Assisted respiration is even worse: here the muscles themselves and the type of respiration make exposure extremely difficult.

Epidural block aims to paralyse the parasympathetic sacral outflow with minimal sympathetic block and thus avoid too great a fall in blood-pressure and yet obtain good constriction of the prostatic bed. Sympathetic tone in the worst-risk cases of elderly patients with cerebral and coronary atheroma may be present.

To limit the sympathetic block to safe levels, one must assess very carefully how high to extend the sensory block. Any slight discrepancy of anæsthesia may be overcome with light general narcosis, and this usually concerns only the skin incision.

These poor-risk and often elderly hypertensive patients receive 15–20 ml. of 1·2% xylocaine, with 1 in 200,000 adrenaline, in the space between the 3rd and 4th lumbar vertebræ. The table is held horizontal as long as the blood-pressure does not fall too much. Spread towards the dorsal region will follow if the table is tilted head down, at the expense of the sacral area. Such a dose gives little more than an hour's anæsthesia in many cases and extends 4–5 segments on either side of the injection. Bleeding is diminished if only because of a diminution in venous return due to loss of skeletal tone from the complete sensory block. The total dose of xylocaine is less than with the technique of spinal and abdominal field block described. Light general narcosis by means of an endotracheal tube prevents CO_2 build-up, yet increases the tidal volume and obviates stagnant anoxia.

It is generally agreed that a wide-bore tube in the trachea helps to reduce oozing from cut tissues.

Even mild degrees of respiratory obstruction with a lowered blood-pressure can produce medullary failure and cardiac ischæmia.

Wound hæmatoma and infection can be avoided if the blood-pressure is allowed to return to normal gradually, which it usually does as soon as the light general anæsthesia is removed.

Regarding reactionary hæmorrhage, close cooperation between surgeon and anæsthetist is essential. The surgeon must attend to every vessel that bleeds. Those that are more readily seen are ligated; others seal themselves with gentle technique and minimal swabbing.

Clot retention with this technique is far less common than with general anæsthesia, because there is less bleeding at operation and after. Here the question of the head-down position is of interest. Unless the prophylactic treatment of spinal headache has changed recently, a head-down tilt is advised for from 12 to 24 hours after operation under spinal analgesia. But after prostatectomy a head-down position should be maintained for only as long as the blood-pressure takes to return to a satisfactory level; otherwise clot retention may be encouraged from a collection of blood in some relatively insensitive area of the bladder wall, such as the posterior wall, which may become firmly organised and cause obstruction to the passage of urine. There will then be increasing distension with urine and clot, followed by bladder spasm and severe pain, with shock out of all proportion to the amount of blood-loss. The foreign body in the bladder then does nothing to prevent further bleeding but actually interferes with the normal mechanism for arresting hæmorrhage, and it becomes essential to remove the clot.

May I end this letter by expressing my admiration for the clear account of their technique which is, I am certain, desirable and effective in their patients. I definitely jib at performing it upon fat and excitable subjects, though I have seen my colleague, Dr. T. R. Steen, perform it on a number of occasions, supplementing a caudal for the spinal block, the whole simplified by great dexterity applied to a suitably premedicated often anæsthetised patient.

Southmead Hospital, Bristol. W. M. MAIDLOW.

SIR,—In reply to Dr. Rollason's letter of Jan. 3, may we point out that he has inadvertently misquoted our figures? Our analysis was of 340 prostatectomies, not 240 as he states: the overall mortality was therefore 10·9% and not 15·4%.

In assessing results of different anæsthetic techniques for prostatectomy the point we wished to make was that comparable series of cases should be studied. As Dr. Ainley-Walker said in his letter of Dec. 20, our series did not completely fulfil this criterion, and for that reason no attempt was made to draw conclusions of any statistical significance. This point we believe to be particularly important in respect of the preoperative condition of the patients. In the only series [1] quoted by Dr. Rollason where an analysis comparable to ours was carried out, patients were divided into three groups—good, fair, and poor. The mortality of these groups was respectively 3·7%, 16·2%, and 40%. In addition the overall uncorrected mortality (27) of Gardner's 258 cases was 10·5% compared to our 10·9%.

The main purpose of our paper was to describe an anæsthetic technique which we have found useful, which

1. Gardner, E. K. *Anæsthesia*, 1958, **13**, 406.

seems to be inadequately represented in the literature, and which has increased the operability-rate in the poor-risk patient.

H. ELLIS
R. A. L. LEATHERDALE.

Oxford.

HYDROCORTISONE INHALATION IN ASTHMA

SIR,—Dr. Morrison Smith (Dec. 13) reported negative results in a trial of hydrocortisone inhalation in asthmatic children. He rightly points out that such trials should give reliable results both statistically and clinically. I find his statistical method admirable, but even the most excellent statistical methods will not be satisfactory if the dose of the drug used is too small to have an effect on the disorder under investigation. Dr. Smith has given only 5 mg. per day of the hemisuccinate, whilst Brockbank and Pengelly [1] and we,[2] whom he quotes, have used 15 mg. per day of the acetate. Our success with this dose has been confirmed from various other quarters,[3–5] and I suspect that Dr. Smith's failure is due to this low dosage which may have been decreased further by the use of an unsuitable inhaler. The droplet size delivered by the inhaler (which Dr. Smith does not specify) is of the greatest importance for the penetration of the aerosol into the finer bronchi. Many commercial nebulisers deliver their output in large droplets which are deposited in the pharynx or trachea and never reach the finer air passages. In such a case the effective daily dosage of hydrocortisone would have been still lower than 5 mg.

London, N.3. H. HERXHEIMER.

PENETRATING THE HOMOGRAFT BARRIER

SIR,—Your leading article last week is timely but in some particulars rather maladroit.

It is, for example, curiously selective to quote only the experiments of Porter and Murray [6] to support the theory of bone-marrow recolonisation, when the work of Lindsley et al.[7], of Ford et al.[8], and of Nowell et al.[9], using respectively red-cell antigens, chromosome markers, and the leucocyte phosphatase reaction, were all published previously and are perhaps to be preferred as evidence.

Secondly, it is quite untrue to say that all mice with surviving mouse-marrow implants die within four months. Such a state of affairs would indeed discourage all therapeutic efforts.

No mention is made of the possibility of homograft "enhancement". The use of prior injections of lyophilised tissue to enhance the survival of normal cells has been demonstrated by Parkes,[10] using the rat ovary, and there are suggestions of a similar effect with skin grafts.[11 12]

Finally, you refer to the "*prospect* of providing a store . . . of frozen embryonic tissues for treating irradiation casualties". Such a store* has been in existence at this hospital for over a year, during which time hæmopoietic tissues have been supplied to six London hospitals and to centres as far apart as Portsmouth and Edinburgh. Most of the cases so treated have suffered from idiopathic aplastic anæmia, but unfortunately, and in common with the experience of Tocantins, no permanent benefit, such as was claimed by Dameshek in four out of twelve cases, has been obtained.[13] An incidental advantage of a centre of this sort, which receives well over a hundred fœtuses a year, is that workers in many different fields of research have access to a reasonably steady supply of fœtal tissues.

Royal Marsden Hospital, London, S.W.3. H. E. M. KAY
M. CONSTANDOULAKIS.

*** We are obliged to Dr. Kay and Dr. Constandoulakis for enabling us to record this application at the Royal Marsden Hospital of the principles that were discussed in our leader.—ED. L.

1. Brockbank, W., Pengelly, C. D. R. *Lancet*, 1958, i, 187.
2. Herxheimer, H., McAllen, M. *ibid.* 1956, i, 537.
3. Lake, C. F., Logan, G. B., Peters, G. A. (1957) *Proc. Mayo Clin.* 1957, **32**, 641.
4. Morris-Owen, R. M., Truelove, S. C. *Brit. med. J.* 1958, i, 969.
5. Hajos, M. *Allerg. Asthma*, 1956, **2**, 363.
6. Porter, K. A., Murray, J. E. *J. nat. Canc. Inst., Wash.*, 1958, **20**, 189.
7. Lindsley, D. L., Odell, T. T., Tausche, F. G. *Proc. Soc. exp. Biol., N.Y.* 1955, **90**, 512.
8. Ford, C. E., Hamerton, J. L., Barnes, D. W. H., Loutit, J. F. *Nature, Lond.*, 1956, **177**, 452.
9. Nowell, P. C., Cole, L. J., Habermeyer, J. G., Roan, P. O. *Cancer Res.*, 1956, **16**, 258.
10. Parkes, A. S. *Trans. Bull.*, 1958, **5**, 45.
11. Billingham, R. E., Sparrow, E. M. *J. Embryol. exp. Morph.*, 1955, **3**, 265.
12. Billingham, R. E., Brent, L., Medawar, P. B. *Trans. Bull.*, 1956, **3**, 84.

* Now supported by a grant from the Medical Research Council.

13. *Blood*, 1958, **13**, 1096.

Obituary

HUGH CRICHTON-MILLER

M.A., M.D. Edin., M.D. Pavia, F.R.C.P.

Dr. H. Crichton-Miller, the founder of the Tavistock Clinic, died at Harrow-on-the-Hill on Jan. 1 at the age of 81. He was a pioneer of his specialty in this country, and those who have come after him are still impressed by his early understanding of the importance of preventive psychological medicine.

Press Portrait Bureau

Born at Genoa, where his father, the Rev. Donald Miller, D.D., was Presbyterian chaplain, he was educated at Fettes College, Edinburgh, and at Edinburgh and Pavia Universities. He qualified in 1898. After holding house-appointments at Edinburgh Royal Infirmary he spent ten years in general practice, in summer at Aviemore and in winter at San Remo. He then decided to specialise in psychotherapy and opened Bowden House, Harrow-on-the-Hill, as a nursing-home for functional nervous disorders. This new approach to the treatment of neurosis claimed his interest till shortly before his death.

In the 1914–18 war he was in charge of functional nervous cases at the 21st General Hospital in Egypt, with the rank of lieut.-colonel, and he was also consulting neurologist to the 4th London General Hospital. The attention paid to shell-shock during the war created a demand for the treatment of psychoneurosis and similar disabilities. To meet this need he founded and became the honorary director of the Tavistock Clinic.

He was vice-president and a member of the executive committee of the National Association for Mental Health and also a member of the International Committee for Mental Hygiene. He became chairman of the medical section of the British Psychological Society and later president of the psychiatric section of the Royal Society of Medicine and president of the International Society for Psychotherapy. In 1938 he was Charles Hastings lecturer of the British Medical Association. Between 1939 and 1941 he was in charge of the E.M.S. Psychiatric Hospital at Stanborough, Watford. Beyond the age to return to the Army himself, he encouraged the members of the staff at the Tavistock Clinic to join one or other Service, and many of them did so. One of the two consultants in psychiatry to the Army, and five out of six of the command specialists in psychological medicine, were drawn from the staff of the clinic.

As a writer he had an easy style with special skill in expounding the complexities of psychology for the educated public.

In 1912 he published *Hypnotism and Disease*, which compares favourably with some of the later and more spectacular contributions to the literature of hypnotism. He soon gave up hypnosis for what he regarded as more enduring methods of treatment for psychoneurotic patients. *Functional Nervous Disease*, edited by him in 1920, had a good reception. From 1922 onwards he published a series of books on the application of the "new psychology" to family life and to the work of educationists. *Insomnia: an Outline for General Practitioners* was published in 1930, *Marriage, Freedom, and Education* in 1931, and *Psycho-Analysis and its Derivatives* in 1933.

The scope, originality, and effectiveness of his contribution to psychological medicine is shown by the following recollections by colleagues:

After many years in general practice with an increasing interest in psychological medicine, and after nine years' experience of running a nursing-home for patients, Dr. Crichton-Miller decided that a clinic for those who were impecunious must be started. The Tavistock Clinic was the result. Starting with four colleagues, he aimed to provide for those who could afford nothing, or the maximal fee of 5*s*. per visit, treatment which was comparable to what they would have been able to get in private in Harley Street. Not unnaturally the work of the clinic grew rapidly, and more staff were found, so that by 1939 some 90 doctors were working there and providing psychotherapy for some 30,000 hours per year. From the beginning it had a children's department—indeed the first patient to be seen there in 1920 was a child. In 1926 a social worker and psychologist were introduced and the first child-guidance team in this country was created, soon to be followed by the child-guidance training centre.

From the beginning the clinic was eclectic in its approach. As its staff grew, it had trained psychoanalysts, psychotherapists of different schools, and one physician who specialised in treatment by suggestion. There was an appointments system for all patients, and the clinic staff, who were all unpaid, worked at hours which fitted in best with the needs of those patients who were employed during the day. Treatment sessions would often begin at 8 A.M. and the last ones might begin at 10.30 P.M. Dr. Crichton-Miller early arranged for teaching courses for general practitioners at the clinic and also introduced distinguished lecturers from overseas. C. G. Jung, Alfred Adler, Ira Wile, and William Healy were among those who gave courses, lectures, and demonstrations. More and more, as the clinic became known, visitors from abroad went back to their own countries to reproduce something of the same type of organisation and atmosphere, so that it is still quite common to find a psychotherapeutic clinic in Scandinavia or in the United States where even the case-sheet used for consultations is a replica of that used at the Tavistock Clinic.

With the opening of outpatient clinics for psychiatric patients in London it was thought that the demand on the services of the Tavistock Clinic might diminish, but in fact the opposite happened and the waiting-list became one of the major problems. In 1932 the clinic was moved to reconstructed premises in Malet Place, where "Parkinson's Law" seemed to operate, for within a short time all the consulting-rooms had to be divided to make more space for more doctors to see their patients.

The inspiration of Dr. Crichton-Miller in starting the clinic was a remarkable venture of faith. He personally carried the responsibility for its finances for the first year, and from then on by devious means it acquired sufficient funds to keep itself out of bankruptcy. Later a hostel was started because he had always had the concept of a non-profit-making organisation which would provide the best quality of outpatient treatment for those who needed to be away from their homes and nearer their place of treatment, and he had ultimately planned and hoped that it might be possible to link it up with Bowden House at Harrow so that there might be facilities for those patients who had to be resident in a hospital.

Along with the concept of careful thorough treatment—some patients attended as many as 600 hours and the average for all patients was 26 hours—Dr. Crichton-Miller recognised the need for teaching and research. His own careful supervision of younger colleagues who were learning how to deal wisely with patients was masterly. He had the gift for delegation of responsibility. His teaching, through lectures and in case discussions, was something which none of those who worked with him are likely to forget. J. R. R.

For all of us who have been engaged in psychiatry—and I started at Hill End in 1919 after my return from the war—Crichton-Miller was a stable and reliable guiding mark, like a lighthouse firmly set in the midst of many cross-currents of psychiatric controversy. He illuminated without obtruding himself, listened and approved, or amended, but always with tolerant understanding and a desire for truth beyond the confines of personal opinion. He was of course a worker, not a dreamer, as the record of his life fully demonstrates. One meets few such men. W. J. T. K.

H. C. M. had a natural gift of exposition and he became widely known as a lecturer in medical conferences, devoting himself particularly to the application of psychology in general practice. His experience as a general practitioner was of special value in the '20s in helping him to maintain a balance between the claims of the enthusiasts for psychological analysis and its equally enthusiastic opponents. At Bowden House and at the Tavistock Clinic he laid down a standard, maintained ever since, of thorough physical examination and treatment, without which no patient was accepted for psychological medicine.

At times he could be a very provocative speaker, and feelings often ran high at the meetings of the psychiatric section of the Royal Society of Medicine. Yet he maintained an open mind, always ready to adopt new methods provided they reached his standard of clinical efficiency.

Crichton-Miller was the pioneer of psychotherapy in this country, and through his work in this field he became known internationally. He propounded an entirely new approach to what is now known as dynamic psychology, and his influence, through his pupils, extends to every part of the world. He was essentially friendly, quite uninterested in formalities; by his charm and sincerity he endeared himself to a large circle of friends. E. A. B.

Crichton-Miller liked to declare himself an eclectic. It was a fair self-description, and carried with it the usual risks—eclectics often seem facile in trying to reconcile elements in opposing theories that are essentially irreconcilable. Crichton-Miller's eclecticism, however, seemed to derive more from his central desire to turn very diverse contributions to practical account in treatment than from any interest in systematic theory. He brought into the period after the 1914–18 war a missionary conviction that psychological treatment should be made much more widely available. He created the Tavistock Clinic to fulfil this purpose; and he had the tolerant range, the background, shrewdness, and unconcern about doctrinal niceties that enabled him to direct it with purposeful enthusiasm. Like Millais Culpin and T. A. Ross and others of his generation who left their mark on British psychiatry, he had no formal training in this branch of medicine, nor in psychoanalysis: he kept free of any close attachment to this or that tradition or approach. He aimed at a synthesis—as between Freud's teachings and Jung's, between somatic pathology and psychopathology, between religion and medical psychology. This hope made him sympathetic to such premature efforts at synthesis as those of Prinzhorn and van der Hoop. His bent was indeed towards sympathy and receptiveness rather than critical examination. He was a friendly man. His charm and considerateness in any joint undertaking were evident when one worked with him on a committee or in a medical society, just as they doubtless were to those who enjoyed the opportunities for work and like-minded contacts that he provided at the Tavistock Clinic. A. L.

Dr. Crichton-Miller married Eleanor Jean Campbell, daughter of Sheriff Lorimer, K.C., of Edinburgh. She died in 1954. They had four daughters and two sons. The younger was killed in a bombing raid over Germany; the elder is now headmaster of Stowe.

EDWARD MANSFIELD BROCKBANK

M.B.E., M.D. Vict., F.R.C.P.

Dr. E. M. Brockbank, honorary consulting physician to the Manchester Royal Infirmary, died on Jan. 2 at the age of 92.

He was born in Geelong, Australia, of Quaker stock. He was educated at Bootham School, York, and at the Victoria University of Manchester, graduating M.B. in 1890. He held various posts at the old Infirmary and Ancoats Hospital and he was the first graduate of the university to be admitted to the membership of the Royal College of Physicians of London. He was elected to the honorary staff of the Manchester Royal Infirmary in 1905 and was active in the wards until 1926 when he retired. He was elected F.R.C.P. in 1907.

His main interests lay in the study of diseases of the heart and in undergraduate teaching, in which he took great pains to instil the basic fundamental methods of clinical examination. It was characteristic of him that he preferred a long monaural stethoscope to the binaural variety. He used to say it kept him out of range of the fleas, which were prevalent on the outpatients of his time, but there was no doubt that with its aid he could hear more accurately than most people could through the modern instrument.

He was a prolific writer of books and articles. His most successful were a book on heart sounds and murmurs which ran into six editions, a book on life-assurance examinations which is still in demand, a history of the lives of the physicians and surgeons on the Infirmary staff up to 1832, and one of the best accounts ever written of Manchester and its institutions.

He was keenly interested in the Manchester Medical Society, and he became chairman of its library committee in 1906. It was he who negotiated the transfer of this large and valuable library to the care of the university in 1930, and he continued in the chair of the university medical library committee until 1951.

Another great interest was the prevention of cancer. For 20 years he was chairman of the research subcommittee of the Manchester Committee on Cancer, which did so much to lessen the frequency of mule-spinners' cancer. The most dangerous oils were identified and advice was given to use only those that were comparatively safe, and the mule-spinners themselves were urged to seek early treatment.

Dr. Brockbank's good looks and white hair gave him a distinguished appearance, and he must have been the last consultant in the city who never owned or drove a motor-car. His conversation and reminiscences enlivened many an unknown neighbour's bus journey to and from their work. A generation of his colleagues, themselves no longer young, will recall him in the years when he was physician and dean at the Infirmary. One of them, T. H. O., writes:

"We have a memory of a tall distinguished-looking man who devoted himself wholeheartedly to his hospital and to our welfare. He played a prominent part in innumerable committees concerned with the medical school and the Manchester Medical Society. He always took a very human interest in those who were under him and was anxious to keep in touch with them in after-years, even when he himself had reached an advanced age. Among his many publications was a book on cardiac murmurs, and he was interested in and encouraged research on cancer and diseases of the heart. When the electrocardiograph was introduced he took an active part in the creation of a department of cardiology.

"Belonging to a generation in which medicine was beginning to emerge from an art into a science, he appreciated the coming of a new era, and medicine in Manchester will remember him with gratitude and appreciation."

Dr. Brockbank's son, Dr. William Brockbank, who has shared many of his father's interests, has followed him in Manchester both as a physician and as a dean.

D'ARCY POWER

C.B.E., M.C., M.R.C.S.

Air Vice-Marshal D'Arcy Power, who retired from the medical branch of the Royal Air Force in 1946, died at his home at Kingston-on-Thames on Dec. 26.

He was born in 1889, the elder son of the late Sir D'Arcy Power, F.R.C.S. From the Merchant Taylors' School he went to St. Bartholomew's Hospital, where he qualified in 1914. While still a medical student he served with the Montenegrin contingent of the British Red Cross during the Balkan war, and he was already a member of the R.A.M.C. special reserve in 1914. Soon after war broke out he was sent to France; he served there and in Belgium, and was awarded the M.C. for gallantry. In 1918 he transferred to the R.A.F. medical branch.

Walter Stoneman

From 1930 to 1934 he was principal medical officer, Mediterranean; in 1942 he became P.M.O. India and South East Asia commands, and in 1945 P.M.O. transport command. In 1945 he was appointed C.B.E. In the first years of his retirement he was house-governor of the Royal Masonic Hospital in London. When he gave up this appointment in 1949 he continued to serve on varied committees, ranging from the British Medical Association council to the executive committee of the Samuel Pepys Club. He was also a foundation member of the College of General Practitioners.

H. E. W. writes:

"D'Arcy was an outstanding medical officer in the Royal Air Force at all stages of his career. He had a presence, was large of build and heart, hardworking, meticulous, reliable, and practical. In addition, he was blessed with a sense of humour, loved good food and wine, and enjoyed the associated good company. An inveterate smoker, he was inseparable from his pipe, which, when not in his mouth, he used to punctuate his statements or to mark the wall behind his chair. He was a dynamic and indefatigible worker, who infected his colleagues and staff with his enthusiasm to attain and maintain the highest standards of work and efficiency. Never more so than when he was principal medical officer of the R.A.F. command in India and South East Asia during the last years of the war. Before the war, when he was at the Air Ministry, he revised and modernised the standards of medical fitness for flying staff, and he played an important part in reorganising hospital catering in the R.A.F., so that it was second to that of no other hospital in this country. Those of us who served with him have lost a loyal colleague and staunch friend."

Air Vice-Marshal Power's wife died last year, and he leaves a son and daughter.

EDWARD JOSEPH COLLINS

M.B. N.U.I., M.Ch. Dubl., F.R.C.S., D.O.M.S.

Mr. Edward Collins, surgeon to the ear, nose, and throat department of Selly Oak Hospital, Birmingham, died on Dec. 20 from a heart attack while he was out shooting, on a visit to his native district of Roscommon. He was 57 years of age.

Educated at Summerhill College, Sligo, he qualified from the National University of Ireland in 1923. After 7 years in general practice he held resident appointments in London at the Royal Marsden Hospital, the West London Hospital, St. Mary Abbot Hospital, and Hammersmith Hospital.

He took the F.R.C.S. in 1934, and two years later the M.CH. Dubl. In the early part of the late war he worked as a general surgeon in the E.M.S. in Birmingham, and in 1942 he joined Mr. Philip Reading in the ear, nose, and throat department of Selly Oak Hospital.

A. M. N., a Birmingham colleague, writes:

"Widely and wisely read, Ned Collins had a prodigious memory and never forgot the lessons he gleaned from the written word, and above all from the many masters of surgery with whom he had come into contact. A first-rate raconteur, he had the ability to create for his listeners vivid pictures of personalities and incidents, and it is a great pity he did not turn his hand to writing down his thoughts and thus leave a more permanent record of his brilliant descriptive powers.

"Those of us who came to know him more intimately, inevitably became admirers of his character and great abilities. His opinion on anything connected with ear, nose, and throat work was highly valued, and his keen powers of observation and deep interest and knowledge of other spheres of surgery often proved useful to his colleagues. He was a man of absolute integrity, possessed of a penetrating and analytical mind which enabled him to reach quickly the crucial point of any problem. He always found time to interest himself in other people, and though he was essentially of a quiet and retiring nature, many were glad to confide in him and seek his guidance.

"A confirmed bachelor, he lived in the hospital during his years at Selly Oak, and his ever-ready presence and help were a great source of comfort to the resident staff. He will be greatly missed by his colleagues, patients, and friends."

J. C. recalls earlier days in Ireland and London:

"Ned Collins and I first met in Galway long ago, and during the years we both lived in London we saw much of each other. He was a man of exceptional ability if, perhaps, a little lacking in wiliness and patience. An athlete in youth, he was of splendid physique and of enormous courage and application. He had the inestimable advantage of being a countryman, for it is the countryman alone who sees life in perspective. As such, he was not addicted to enthusiasms of any kind.

"This old companion on the road of life (and we walked many roads together) was a fine, dependable man. And he received at least one of the measures of good fortune wished in the ancient toast—death in Erin."

SELINA FITZHERBERT FOX

M.B.E., M.D. Durh.

ON Dec. 27 Dr. Selina Fox died at the Bermondsey Medical Mission, which she had founded in 1904. She was 87 years of age.

She was the daughter of Sir Francis Fox, the well-known railway engineer. She studied medicine at the London School of Medicine for Women and at Newcastle upon Tyne. After qualifying in 1899 she went to India to work for the Zenana Bible and Medical Mission at the Lady Kinnaird Hospital in Lucknow. But her health was not able to withstand the climate, and the following year she returned to England where she began her work in Bermondsey as medical officer of the training school of the Church Missionary Society. In 1904 she founded the Bermondsey Medical Mission in a house in Grange Road. The work grew rapidly, and besides offering comfort and help to the poor of the neighbourhood the Mission became a valuable training centre.

In 1914 Dr. Fox was appointed deputy governor of the women's prison at Aylesbury and to the borstal institution for girls there. Later she was promoted to be governor; but while holding this appointment she continued her work in Bermondsey, and after the war she returned to spend all her time there. Soon afterwards the nucleus of the present hospital was formed when she opened a ward with half a dozen beds in an Army hut in the garden of the Mission. The venture won support and contributions; and in 1929 the hospital, with its own small chapel, was formally opened.

B. M. writes:

"When I joined the staff of the Bermondsey Medical Mission, Dr. Fox had already ceased to do any clinical work, but one was aware that her work among the women and children in Bermondsey in the early days had left its mark. Even now the older patients in the clinics tell not only of her medical care, but also of her kindness in helping them with clothing, with food from the soup kitchen, and even by pulling out their teeth without an anæsthetic. It was always her policy to charge a few pence, so that there would not be carelessness in the use of the Mission's services. When I came patients paid 2*d*. to see an "ordinary" doctor and 6*d*. to see a specialist. Many were the tales Dr. Fox told us of dirt and bugs, overcrowding, poverty, and drunkenness in those early days. These were the times when women wore shawls and clogs, and Dr. Fox's umbrella, her almost inseparable companion, was one of the first in the neighbourhood. She was a typical pioneer medical and social worker, friendly towards other welfare organisations, but always working on individual lines. She had a great interest in building, inherited from her father, and she was never happier than when planning new buildings or adapting old ones.

"The transfer of the hospital to the National Health Service in 1948 gave her great cause for anxiety lest its religious character should be lost. Her fears proved unfounded and, though she was never quite reconciled to the new regime, she was greatly relieved to find that the Mission not only continued alongside the transferred hospital but was able to develop along new lines by providing clubs and convalescent and permanent homes for the elderly.

"Dr. Fox came back to live in Bermondsey in 1946, and, until she was admitted to the hospital as a patient in 1955, she was a daily visitor in the wards, speaking to each patient and regaining the contact with the local people which she had lost a little in the intervening years. She had a tireless and indomitable spirit, and she was indefatigable in her efforts to raise the funds to keep the work going. Orthodox and sincere in her Christian profession, she was one of the last of the generation of pioneer workers who played so important a part in the social improvements seen in this century."

Appointments

BEYNON, PEGGY, M.R.C.S., D.P.H.: assistant M.O., Surrey.

BOLTON, F. G., M.D. Brist., M.R.C.P.: consultant clinical pathologist, Churchill Hospital, Oxford.

GRAHAM, J. A. G., M.B. Edin., D.P.H.: deputy M.O.H. and deputy principal school M.O., Croydon.

ISAAC, R. G., M.R.C.S., assistant M.O., Dumfriesshire.

MILNE, H. B., M.B. St. And., D.PSYCH.: senior assistant psychiatrist, Pastures Hospital, Mickleover, near Derby.

ROBINSON, J. O., M.D., M.CHIR. Cantab., F.R.C.S.: consultant general surgeon, Chalfonts and Gerrards Cross Hospital, Chalfont St. Peter, Buckinghamshire.

TURNEY, J. P., M.B. Lond., F.R.C.S.: senior casualty officer, West Cumberland group of hospitals.

WHEILDON, ALICE, M.B. Melb., M.R.C.O.G.: senior assistant M.O., Hornsey and Tottenham.

WYNFORD-JONES, H., M.R.C.S.: senior casualty officer, Mansfield and District General Hospital, Nottinghamshire.

Manchester Regional Hospital Board:

ANDERSON, J. P., M.D. Durh., M.R.C.P.E., D.C.H.: assistant physician and deputy medical superintendent, Monsall Hospital, Manchester with duties at Ladywell Hospital, Salford.

FERGUSON, R. S., M.D. Glasg., D.P.M.: part-time consultant psychiatrist, Blackpool and Fylde and Lancaster Moor groups of hospitals.

MILLER, R. S., M.R.C.S., D.M.R.D.: consultant radiologist, Wigan and Leigh group of hospitals.

Colonial Appointments:

CHAN-LI, H. Y., M.B. Sheff.: M.O., Mauritius.
FUNG, JOYCE, M.B. Brist., M.O., British Guiana.
HUTCHISON, RONALD, M.B. Edin.: M.O., northern region, Nigeria.
LAMBIE, JAMES, M.G. Glasg.: M.O., Hong Kong.
MCINTYRE, J. C., M.B. Edin.: M.O., Sierra Leone.
RICHARD, D. R., B.M. Oxon., F.R.C.S.: orthopædic registrar, northern region, Nigeria.
SAGAR, M. B., M.B.: M.O., British Guiana.
TAYLOR, T. J., M.B. Lond.: assistant M.O., Bahamas.
TEMPLE, D. E. L., M.B. Edin.: assistant M.O., Bahamas.
WHEELWRIGHT, D. A., B.M. Oxon.: Government M.O., Bermuda.

Notes and News

PRESCRIBED INDUSTRIAL DISEASES: RIGHT OF APPEAL

A RIGHT of appeal from medical boards' decisions on whether a person claiming benefit under the industrial injuries scheme has one of certain prescribed industrial diseases is provided by regulations [1] made by the Minister of Pensions and National Insurance. The regulations will apply to decisions given by medical boards on or after Jan. 5, 1959. Appeals by claimants will be decided by medical appeal tribunals, which will also consider decisions referred to them at the instance of the Minister. The tribunals, each of which consists of doctors of consultant status sitting with a legal chairman, already consider appeals against medical boards' assessments of the extent of disablement due to an industrial accident or disease.

University of London

Dr. J. H. M. Pinkerton, senior lecturer at the University College of the West Indies, has been appointed to the second chair of obstetrics and gynæcology at the Institute of Obstetrics and Gynæcology.

Dr. Pinkerton graduated M.B. from the Queen's University, Belfast, in 1943. He took the M.D. two years later and the M.R.C.O.G. in 1950. He held the appointment of senior tutor in obstetrics and gynæcology at the Queen's University before going to the West Indies.

Mr. W. G. MacGregor, senior lecturer at University College Hospital Medical School, has been appointed to the readership in obstetrics and gynæcology at the institute.

Order of St. John of Jerusalem

The Queen has sanctioned the following promotions in, and appointments to, this Order.

As Knights.—E. H. Lodge, M.B., M. M. Scott, M.R.C.S., Lieut.-General Sir Alexander Drummond, K.B.E., C.B., LL.D., F.R.C.S.

As Commanders (Brothers).—Major-General W. E. Tyndall, C.B., C.B.E., M.C., M.B., E. J. G. Wallace, M.B., Colonel R. G. W. Ollerenshaw, T.D., B.M., Major H. C. Stewart, M.D., D. A. B. Hopkin, M.D., F.F.A. R.C.S., C. L. Worthington, M.B.

As Officers.—Major M. S. Harvey, M.B., J. A. Tomb, M.B., James Orr, M.B., D. W. Hendry, M.D., T. K. Elliott, M.B.

Public Health and the Family Doctor

The College of General Practitioners and the Society of Medical Officers of Health will hold a joint conference on this subject on Saturday and Sunday, May 23 and 24, at the Wellcome Building, Euston Road, London, N.W.1.

The themes chosen for discussion are the new epidemiology, family health, and partners in social medicine. The speakers will include Dr. G. I. Watson, Dr. J. F. Warin, Dr. Jean Mackintosh, Dr. John Fry, Dr. R. J. F. H. Pinsent, Dr. J. D. Kershaw, and Prof. C. Fraser Brockington. Further particulars may be had from Sir Selwyn Selwyn-Clarke, secretary of the Society of Medical Officers of Health, Tavistock House South, W.C.1.

Ministry of Pensions and National Insurance

Sir Arthur Massey, chief medical officer of the Ministry, is retiring on March 31, and Dr. C. G. Magee, a deputy chief medical officer in the Ministry, has been appointed to succeed him.

Dr. Magee received his medical training in the medical schools of Glasgow, Edinburgh, and Manchester. After house-appointments at Glasgow Royal Infirmary, Ancoats Hospital, Manchester, and Salford Royal Hospital, and a spell of ten years in general practice, he came to London where he commenced practice in accident insurance work, specialising in head injuries and other neurological traumata. He became M.R.C.P.E. in 1933 and was elected F.R.C.P.E. in 1940, in which year he joined the former Ministry of Pensions as a medical officer; he became deputy director-general of medical services in 1947. On the merger of that Ministry with the Ministry of National Insurance in 1953 he became one of the two deputy chief medical officers in the new Ministry of Pensions and National Insurance. Dr. Magee's published papers include a study of spontaneous subarachnoid hæmorrhage. He was a member of the Piercy Committee on the rehabilitation, training, and resettlement of disabled persons in 1953. He was appointed Q.H.P. in 1957.

1. National Insurance (Industrial Injuries) (Prescribed Diseases) Amendment (no. 2) Regulations, 1958; S.I. 1958 no. 2112. *3d.*

Royal Society

Sir Lindor Brown and Sir Charles Dodds have been appointed vice-presidents of the society for 1958-59.

Release of Viomycin

The Ministry of Health, in conjunction with the Department of Health for Scotland, has made arrangements with British suppliers of viomycin which will enable this antibiotic to be prescribed by doctors in this country from Feb. 1, 1959.

A clinical meeting of the Airborne Medical Society will be held at Hammersmith Hospital, Ducane Road, London, W.12, on Friday, Jan. 30 at 6 P.M.

Diary of the Week

JAN. 11 TO 17

Monday, 12th

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W.12
4 P.M. Dr. W. S. C. Copeman: Management of the "Rheumatoid" Patient.

Tuesday, 13th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.1
5 P.M. Dr. H. R. Vickers: Place of Dermatology in a General Hospital. (Watson Smith lecture.)
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8 P.M. *Psychiatry.* Dr. Max Hamilton, Dr. J. M. White, Dr. C. M. B. Pare: Investigation of Outcome of Treatment.
KING'S COLLEGE HOSPITAL MEDICAL SCHOOL, Denmark Hill, S.E.5
4.30 P.M. Mr. Hedley Atkins: Modern Aspects of the Treatment of Cancer of the Breast. (Dorothy Platt lecture.)
ST. MARY'S HOSPITAL MEDICAL SCHOOL, W.2
5 P.M. Mr. A. W. Badenoch: Pyelitis of Pregnancy.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. Brian Russell: Tuberculosis and Tuberculides.
MANCHESTER MEDICAL SOCIETY
5 P.M. (Medical School, University of Manchester.) Prof. J. S. Mitchell: Some Newer Developments and Ideas in Radiotherapy.

Wednesday, 14th

POSTGRADUATE MEDICAL SCHOOL
2 P.M. Dr. H. A. Sissons: Bone Structure and Bone Disease.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. Henry Haber: Histopathology of Vesicular and Bullous Eruptions.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Mr. N. R. Barrett: Foreign Bodies in the Venous System.
ROYAL MEDICO-PSYCHOLOGICAL ASSOCIATION
8 P.M. (11, Chandos Street, W.1.) Dr. Jonathan Gould: Hypnosis and the States of Altered Awareness.

Thursday, 15th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
3.45 P.M. Dr. B. Cohen: Modern Variations of John Hunter's Madder Feeding Experiments. (Arnott demonstration.)
ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, 26, Portland Place, W.1
7.30 P.M. Dr. P. E. C. Manson-Bahr: East African Kala-azar, with Special Reference to the Pathology, Prophylaxis and Treatment.
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Prof. M. Maizels: Place of Chemical Pathology in Medicine.
BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street, W.1
8 P.M. Mr. Rodney Smith; Mr. Eric Samuel: Cholongiography.
WEST OF ENGLAND CHILD HEALTH GROUP
8.30 P.M. (Children's Hospital, Bristol.) Prof. A. I. Darling: Preventive Dentistry.
MANCHESTER MEDICAL SOCIETY
8 P.M. Dr. A. D. Clarke: A Search for the Perfect Endotracheal Tube.
LIVERPOOL MEDICAL INSTITUTION, 114, Mount Pleasant, Liverpool, 3
8 P.M. Professor Mitchell: Mechanisms of the Therapeutic Actions of Radiations.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Physiology Department, Dundee.) Prof. Eric Neil: Reflexogenic Areas of the Cardiovascular System.

Friday, 16th

ROYAL SOCIETY OF MEDICINE
5.30 P.M. Air Marshal Sir James Kilpatrick: The Growth of an Organisation for Preventive Medicine.
8.15 P.M. Dr. Roy Astley, Dr. Clifford Parsons, Mr. A. L. d'Abreu, Dr. Graeme Sloman: Cine-angiography.
POSTGRADUATE MEDICAL SCHOOL
10 A.M. Mr. G. H. Wooler: Treatment of Hiatal Hernia with Peptic Œsophagitis.
4 P.M. Dr. A. C. Dornhorst: Pulmonary Physical Signs.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
5.30 P.M.: Mr. Gilbert Howells: Orbital Tumours.
PLYMOUTH MEDICAL SOCIETY
8.30 P.M. (Freedom Fields.) Sir Cecil Wakeley: Some Aspects of Malignant Disease.
ROYAL MEDICO-CHIRURGICAL SOCIETY OF GLASGOW
8.30 P.M. (Hall of the Royal Faculty of Physicians and Surgeons of Glasgow.) Dr. Peter Macfarlane and Dr. R. G. Sommerville: Bronchiectasis—a Virus Disease?